# THE NATURAL HISTORY OF CANCER

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WITH

SPECIAL REFERENCE TO ITS CAUSATION AND PREVENTION

BY

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# PREFACE

THE subject of cancer has hitherto been investigated far too exclusively by the pursuit of details in ultimate analysis; and hardly at all by the synthetical and comparative methods, which have been so profitably employed in other branches of biological research.

As that fine pathologist Billroth has remarked: "Everything is too hurried nowadays. We suffer from an insatiable craving for new—or apparently new—facts, in the hope of obtaining a possible sensational success. No time is allowed to reflect upon, or to reconsider, the onward course of scientific inquiry. Where are we? What have we left behind? What is ahead? Is it worth while to go farther in this direction or in that? Has detailed work given us a profitable knowledge of, or an insight into, the whole subject? No one finds time to answer such questions."

In order that the immense stores of miscellaneous items of knowledge accumulated during the last half-century by dispersive analysis, may be profitably utilized for cancer research, concentration is above all things necessary; for only thus can a higher plane of progress be attained.

Moreover, since the cure of cancer altogether transcends present experience, I have in this work specially endeavoured to elucidate the causation and prevention of the disease rather than its cure; for which, in my opinion, reliable indications are lacking.

To this end I have devised and applied a new method of cancer research—which may be called synthetic—whereby I have shown that there are modes of life, various habits and so forth, which tend to prevent the incidence of cancer almost entirely in healthy stocks, and greatly to reduce its ravages, even among those hereditarily predisposed.

Such are the objects to which the present work is dedicated.

W. ROGER WILLIAMS.

CLIFTON, BRISTOL,
*April*, 1908.

## ERRATUM

Page 446, eleventh line from the top:

"as well as in the veins of the lungs, brain," *for* "veins" *read* "bloodvessels."

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# THE NATURAL HISTORY OF CANCER

## CHAPTER I

### INTRODUCTORY

#### The Status of Pathology, and the Meaning of the Term "Natural History" as here Employed.

It may be said of each particular science—as of science in general—that it has been gradually evolved. But this process has affected the various sciences very unequally, so that while some have nearly attained the highest degree of perfection, others are still in a crude, infantile, or undeveloped state.

In accordance with these ideas, the sciences may be classified in a hierarchical manner, according to their state of perfection and degree of evolution, with mathematics and astronomy at one end of the series, and the biological sciences—which include pathology—at the other.

In the intellectual progress of the nineteenth century, the chief event has been the translation of these immature biological sciences from the domain of empiricism, to their proper place in the scientific hierarchy.

So far as pathology is concerned, however, this great movement is still in its infancy; for although the medical art has been practised from time immemorial, it is only since the beginning of the nineteenth century that the crude data thus laboriously acquired, have begun to be treated scientifically. There has been no Comte, Spencer, or Darwin to lighten the darkness of modern pathology. What about Virchow?

It is necessary at the outset to refer thus pointedly to the crudeness and immaturity of medical knowledge, because nowhere do these qualities find more striking exemplification, than in the terrible welter of disjointed facts and contradictory hypotheses, that constitute such a large part of modern "tumour science."

Owing to the progress of knowledge, successive generations view the problems presented by the phenomena of disease from different standpoints—hence every age needs its own interpreters. This is specially true of the vast subject of onkology. It will be my endeavour in what follows to reduce into some semblance of order these vast masses of chaotic materials, and to deduce from them such conclusions as the facts seem to warrant. In doing this I shall not scruple to avail myself of hypotheses, when these seem likely to aid the investigation; for, as Comte says : "Si en contemplant les phénomènes, nous ne les rattachions point immédiatement à quelques principles, non-seulment il nous serait impossible de combiner ces observations isolées, et par conséquent d'en tirer aucun fruit, mais nous serions même entièrement incapables de les retenir ; et le plus souvent les faits resteraient inaperçus sous nos yeux." The history of every branch of medical knowledge teems with illustrations of the truth of this luminous statement.

By all means let pathologists observe and experiment, but let them not neglect to compare, systematize, filiate, and reason on the knowledge thus acquired—in a disinterested way—as if they were dealing with a problem of natural history; and, above all, it must never be forgotten that *comparison* is the great organon of biological, and consequently also of pathological, research.

Hitherto research has been far too exclusively directed to the histological, morphological, and experimental conditions of tumours, while the ensemble of their characters and their inter-relations with other biological processes have been but little studied. The object of the present work is to remedy these defects by giving a right bent to research, and a scientific basis to the pathology of cancer and tumour formation. To effect this we must work on a broader basis than has hitherto been customary. As Bacon[1] has insisted, in dealing with matters of this kind : "The first object must be to prepare a history of the phenomena to be explained, in all their modifications and varieties. This history should comprehend not only all such facts as spontaneously offer themselves, but all the experiments instituted for the sake of discovery or for any other purposes. It ought to be composed with great care ; the facts accurately related and distinctly arranged ; their authenticity diligently examined ; those that rest on doubtful evidence, though not rejected, yet noted as uncertain, with the grounds of the judgment so formed. This last is very necessary, for facts often appear incredible only because we are ill-informed. This record of facts is *Natural History.*"

Such is the method I propose to employ in the present undertaking.

## The Term "Tumour."

It is in consequence of such conditions as those above mentioned, that so many of the leading pathological terms are without precise significance. Thus the word "tumour," by which we connote the various pathological formations with which this work is concerned, has not only been interpreted differently in different ages, but also by authors living in the same age, and this diversity is still apparent. A generally acceptable definition is, I think, hardly likely to be arrived at, until we have attained more uniformity in our conceptions as to the origin and causation of these formations.

By the Latins, who gave us the term, any unusual kind of swelling was called "tumor" ; thus Galen and his followers describe : "Tumores secundum naturam supra naturam et præter naturam." In the first group they included physiological enlargements, in the second swellings

[1] "Novum Organum," ii.

due to displacement of natural parts, while the third embraced all other swellings—a miscellaneous assemblage, comprising all that has since been included under the term "tumour," and many other conditions.

The tendency of subsequent ages has been to restrict the use of this term to a much narrower range. Virchow, however, classed as tumours nearly all chronic inflammatory and granulomatous formations, which are now generally regarded as being altogether outside this category.

Recently the term "neoplasm" has obtained currency as a synonym for "tumour," for which the old Greek word was ὄγκος, whence this study has been designated "onkology."

Many and various are the tentatives that have been made to define the term "tumour," but it cannot be said that any of them are really satisfactory. No doubt John Hunter realized this when he said: "Of all things on the face of the earth definitions are the most cursed"; and Virchow was nearly as emphatic with his famous dictum: "No human being can define, even under torture, exactly what a tumour is." Thus we reach the conclusion that tumours, like other biological conceptions, do not admit of strictly logical definition.

For practical purposes, however, a tumour may be defined as a persistent mass of redundant new formation, not obviously due to any extrinsic cause, which grows independently of the body, with which it is structurally and functionally uncombined; so that, although it generally assumes a more or less circumscribed form, it is nevertheless distinct from any known anomaly.

From the biological standpoint, tumour formation may be regarded as a phenomenon of the same order as reproduction in general—that is to say, as a special form of overgrowth of the individual. This implies recognition of the affinity between tumour formation and morphological variation in general, which has hitherto been generally overlooked, much to the detriment of progress in tumour science. It will be maintained in the sequel that, in ultimate analysis, a tumour is the outcome of an abortive attempt of certain cells to repeat agamically some portion of the normal ontogeny—hence individuation is the cardinal feature of every tumour. What is variation but a novel kind of cell multiplication? And what is tumour formation but a special variety of this novelty? And is not every variation, as suggested by Virchow, essentially pathological in origin? Variation, mutation, and tumour formation—what are these but different degrees of the same process, which, being maintained continuously from the germ to the latest period of life, determines all organic formation? In the sequel it will be shown that the determining factor, the true cause of all these variations, is nutrition—using the term in its widest sense.

Such is the thesis I now propose to maintain.

### Some Generalities de Tumoribus.

In investigating the structure and development of tumours, it is impossible for the observer to escape the conviction that the phenomena met with have their counterparts in the normal evolution. Tumours, like other organic structures, ultimately depend upon the processes of growth and reproduction going on in the cells of the part whence they originate, whether these are of pre- or post-natal origin. Pathological and physiological cells are alike in their morphological and vital properties. Cell and nuclear division conform to the physiological type, even as to the details of karyokinesis. In both cases the tendency of the newly formed cells to revert to the parental type is perfectly obvious, and this is specially manifest when the tumour cells become converted into tissues. Hence the same tumour can only be found again, in exactly the same situation. Thus it happens that throughout the whole range of tumour structures no elements of new and specific type can be found, but we everywhere meet with structures which resemble the physiological structures, both genetically and histologically. In short, tumours are never of such a monstrous nature, as not to present some analogy with the corresponding pre-existing structures of the part whence they originate, either in their embryonic or post-embryonic states. Hence no study of the life-history of tumours can be complete, which ignores pre-existing structural peculiarities.

But behind these structural changes we must remember there always are functional changes, although ordinarily we hear very little of them in connexion with modern studies on tumour genesis. We may, however, be certain that tumours, like other morphological variations, are ultimately the outcome of the interactions of function and structure.

Tumours grow and are nourished like normal parts of the body, yet, in return for the nutriment thus supplied, they contribute to it nothing useful ; indeed, their relation to the rest of the organism differs but little from that of parasitism.

## Malignancy.

Even if pathology were as highly perfected as botany and zoology, pathological classifications would never have the same significance as botanical and zoological taxonomies, because of the instability and mutability of pathological processes and products. Nevertheless, even pathological classifications are useful, if only in that they compel order in our conceptions.

Tumours have been classified on many bases—physiological, morphological, chemical, genetical, ætiological etc. ; but by far the oldest and most generally useful classification is that which divides them, according to their physiological properties, into the *malignant* and *non-malignant*, and for our immediate purpose this will suffice. Here, however, it must be noted that tumours exhibit many degrees of malignancy, both in the plus and minus directions.

In former times certain intractable diseases were commonly called malignant, under the belief that they were due to the special influence of malign or evil spirits, and it is to this superstition that we owe the term as applied to certain tumours.

Even at the present time it is not easy to define the precise signification of this much-used term, which covers a multitude of effects, although, in a general way, its meaning is intelligible enough. Thus, every one understands that malignant tumours are intractable, destructive, and tend to a fatal end; and these results are generally the direct consequences of their malignant properties.

These comprise—(1) persistence, with a tendency to softening and ulceration; (2) an infiltrating mode of growth, so that the margin of the tumour interpenetrates and destroys the surrounding structures; (3) dissemination, by which is meant the power of the primary tumour to form secondary tumours like itself, (*a*) in the vicinity of the primary tumour, (*b*) in the adjacent lymph glands etc., and (*c*) in distant parts of the body, such as the liver, lungs, bones etc.; (4) recurrence, or the power of the tumour to grow again, even after the most drastic attempts to ensure its complete destruction by the knife, fire, caustics etc.; and (5) cachexia, or a certain impairment of the general health with wasting.

It is in the combination of these various properties, rather than in any one of them taken by itself, that malignancy consists, for, as Paget remarks: "Each may be absent in tumours having all the other features of malignancy, and certain of them may be seen occasionally in tumours which, in other respects, appear to be non-malignant." Thus cancer *qua* cancer, gives no specific indication of its presence.

Let us consider this matter a little more in detail.

First of all with regard to the item persistence, it can hardly be maintained that the essence of malignancy lies in it, for intractability is a feature of all tumours, malignant and non-malignant. Moreover, many tumour-like swellings of granulomatous nature may be as intractable as cancer—*e.g.*, certain syphilitic and tuberculous lesions, mycosis fungoides, mycetoma, etc.

A more characteristic feature of malignancy is infiltration, which has often been regarded as distinctive. Processes of the tumour substance interpenetrate the adjacent structures, which they destroy—as it were, by dissolving—and supplant. This mode of increase is wellnigh universal among malignant epithelial tumours—which constitute, according to my estimate, 85·4 per cent. of all malignant tumours—but among the sarcomata it is not so general.

In many "chronic inflammatory" processes infiltration and interpenetration have been demonstrated. Thus, for the uterus, Friedländer and Councilman have shown that the so-called "erosions" of the *os uteri* are, in this respect, often indistinguishable from cancer; and we are now acquainted with many "chronic inflammatory" lesions of the skin and other structures, in which the same phenomena have been noted.

In a general way it may be said that this mode of growth is one of the properties, which cancer shares with immature tissues in general. Thus, even in the course of normal development—pre-natal and post-natal—examples of it often occur, especially in the evolution of glandular and papillated structures, in the conversion of cartilage into bone etc. But perhaps the most apposite physiological prototype of this feature of malignancy is to be found in placenta formation, when the epithelia of the trophoblast and chorionic villi interpenetrate the decidual and maternal tissues and destroy them; and, as we now know, when this process goes beyond certain limits a tumour results which may be either innocent or malignant, according to the special circumstances of the particular case.

No feature of malignant disease has been more frequently regarded as pathognomonic than "dissemination"; yet it is asserted that non-malignant tumours occasionally manifest this property, as well as certain pseudo-plasms of which I shall have more to say in the sequel.

It is difficult to decide as to the validity of the claim to dissemination which has been made for thyroid adenomata, uterine fibroids, certain ovarian cystomata etc. No doubt many cases of this kind admit of being otherwise explained. Nevertheless, recent investigations of the changes taking place in placentation, "deportation of chorionic villi," "hydatid mole," and the disease called "*deciduoma* vel *chorioma*," seem to indicate that there is nothing specific of malignancy merely in "dissemination."

The inference to be drawn from the many instances of malignant disease developing in the track of operation wounds, especially after the removal of non-malignant ovarian and uterine tumours, etc., to which I have specially called attention, is of similar import.

From recent researches as to placentation it appears that, even under normal circumstances, cells of the trophoblast and chorionic villi constantly enter the maternal circulation during gestation, where, as a rule they perish; but, under circumstances not yet determined, they may originate malignant or non-malignant tumours in various more or less remote parts of the body, such as the vagina, vulva, or even in the brain, lungs etc.

There are good reasons for believing that the constituent cells of most malignant tumours are, in like manner, constantly entering the circulation, where, as a rule, they also perish and are absorbed, so that only those endowed with sufficient vitality to overcome this resistance originate dissemination tumours. (Probably not vitality, but numbers)

To account for these phenomena, it is assumed that the circulatory fluids contain some substance (antitoxin, enzyme etc.) inimical to the intruding cells, by virtue of which their destruction is effected; but when, after a time, this protective substance has become used up or so attenuated as to be no longer effectual, these foreign cells then originate tumours. It certainly accords with this view, that secondary tumours are seldom found during the initial stage of malignant disease.

It is also noteworthy that certain malignant neoplasms rarely disseminate—*e.g.*, myeloid sarcoma, glioma, and "rodent ulcer"; moreover, even for the same variety of malignant tumour in the same locality, the degree of dissemination is very variable; and in all parts of the body dissemination is much influenced by the localization of the primary disease. These considerations indicate that the disseminativeness of malignant tumours is, in a measure, conditioned by local structural and physiological peculiarities, which render it easy for their constituent cells to get access to, to live in, and to be transported by, the adjacent lymphatics and bloodvessels.

Recurrence may be regarded as a consequence of dissemination, chiefly of the local kind—that is to say, as a continuation of the disease in surviving unextirpated fragments of the primary tumour or its offsets. Indeed, such is the great tenacity of life and the wonderful proliferative power, of even the most diminutive fragments of malignant tumours that, when any of these are left behind after operation, as is usually the case, they only too frequently become fresh centres of disease.

Just as a *Hydra* regenerates itself after mutilation, and after it has been cut into small pieces, so it is with these malignant tumours.

Viewed in this light, recurrence is, of course, no more specially distinctive of malignancy than dissemination.

It accords with this, that some of the most inveterate and striking instances of recurrence are met with among tumours not otherwise remarkable for their malignancy, such as rodent ulcer, myeloid and spindle-celled sarcomata, keloid etc.

Moreover, non-malignant tumours sometimes grow again after removal, of which examples are furnished by uterine myoma, ovarian cystoma, mammary fibro-adenoma, subungual exostosis, condyloma, warts etc.; and in macrodactyly, even after amputation of the affected part with the phalanges, the giant growth has been known to recur in the previously healthy stump; while the recurrence, after extirpation, of a redundant mammary structure has lately been reported.

The impairment of the general health—cachexia—that is so often associated with malignant tumours, never precedes the outbreak of the primary disease—hence we infer that it is a consequence of their local progress. In confirmation of this it may be mentioned that cachectic symptoms usually disappear for a time, after the removal of the local disease. It is well known that the constituent cells of malignant tumours are remarkably prone to degenerative changes ending in disintegration. It seems probable that, just as dissemination depends upon the entry of living tumour cells into the circulation, so cachexia likewise depends upon the entry into the circulation of the products resulting from their disintegration. These are believed to comprise toxic albuminoids, which, being in quantities too great to be quickly neutralized, poison the system, especially the blood and hæmatopoietic organs.

Cachexia is more frequently seen with epithelioma than with sarcoma, and with some varieties of both forms of malignant disease—*e.g.*, rodent ulcer, spindle-celled and myeloid sarcoma—it seldom occurs. Even among the different varieties of the same form of malignant disease, there are great divergencies as to the occurrence of cachexia; thus it is much more frequently met with in association with cancers whose constituent cells are specially prone to degenerative disintegration (*e.g.*, the ordinary cancer of the breast), than with those whose cellular elements are more stable (*e.g.*, the lip).

A similar condition is sometimes induced by very large non-malignant tumours, especially of the uterus and ovaries; and even by some pseudoplasms, such as mycosis fungoides.

In the constitutional changes coincident with pregnancy and post-partum conditions, we see manifested the physiological counterparts of cachexia.

It follows from the foregoing analysis of the distinctive features of malignancy, that there is nothing new or specific about them ; these effects may, indeed, be ascribed to the exacerbation in some directions, and to the diminution in others, of processes which are of normal occurrence in the various phases of embryonic or post-embryonic life.

Thus malignancy is a relative term, of which there is no absolute morphological or chemical criterion. Indeed, malignancy—like growth—has no specific pathognomonic mark by which it may be certainly discriminated and appraised ; for—like growth—malignancy is essentially a dynamic force, whose presence can only be surmised and estimated by careful weighing of the ensemble of the indications available for its diagnosis—that is to say, by its effects.

What, then, is the anatomical element upon which malignancy depends ? The predominant constituent of all malignant tumours is the cell, and it is to the cell that we must look for the answer to this question. Ever since the discovery of the cellular nature of the body, the cells of malignant tumours have been closely scrutinized, with the hope of finding in them some specific mark, but all in vain. The more thoroughly the examination has been made, the more clearly has it proved the correctness of J. Müller's conclusion that : "The minutest elements of malignant tumours do not differ in any important respect from the constituents of benign tumours, nor from those of the body in its adult or embryonic condition." Such being the case, we can but conclude that there is no specific anatomical element or chemical substance characteristic of malignancy, other than such as occur in the physiological state. From this it may be inferred, that the process which manifests itself in malignancy, and the process of which benign tumours are the outcome, are the same in kind, and that they differ only in degree ; while, in the normal ontogeny, both have their physiological prototypes.

In a general way, it may be said of malignant tumours, as compared with benign ones, that they are, structurally regarded, characterized by immaturity and defective organization. In their structure cells capable of active growth and development predominate. The morbid formation, however, always has a certain likeness to the structure of the part whence it originates—hence malignant tumours of the same kind, but springing from different parts of the body, are by no means identical in structure. What, for instance, can be more divergent in this respect, than the appearances presented by microscopical sections of cancers from such different parts as the breast, the stomach, and the skin ? Moreover, if we pursue the analysis further, we shall find that even special substances secreted by the cells of these organs, are duly represented in the corresponding cancerous products, although the latter are never able to produce a perfect secretion. Thus, more than half a century ago, J. Müller demonstrated the presence of casein in mammary cancers, and the special proneness of the constituent cells of these tumours to fatty metamorphosis is well known. We are thus reminded of the similar changes that the cells of the normal gland undergo, during the elaboration of their peculiar secretion. Of similar import is the cornification of the cells of cutaneous cancers. Waring has specially called attention to this neglected feature of malignant tumours by demonstrating, that the constituent cells of cancers of the stomach and pancreas produce the same special ferments—pepsin, trypsin etc.—as the normal secretory cells of these organs.

With regard to the chemical nature of malignant tumours, it is noticeable that albuminoid materials predominate; and, as in actively growing structures in general, sugar-forming substances abound.

The appearances revealed on microscopical examination of actively growing parts of malignant tumours, on the whole, have a great likeness to those met with during the course of the development of the affected part.

In the case of cancers of glandular origin, the epithelial cells at the seat of disease become unduly numerous, and acquire a multilaminar arrangement, encroaching on the lumen of the gland, which they commonly obliterate. The newly formed cells, for the most part, also often lose their typical shape. Thus the diseased glandular structure is converted into a club-shaped mass of proliferating epithelial cells. Here and there bud-shaped collections of these proliferous cells press on the *membrana propria*, forming solid processes, which interpenetrate the adjacent structures in the directions of least resistance, where they branch and anastomose. By the repetition and further extension of this process the cancerous tumour is formed. In most cases these ingrowing epithelial columns retain their solid form; but exceptionally they eventually develop more or less complete lumina, and otherwise mimic the structure of the gland whence they originated.

In their entirety, the pathological appearances present striking resemblance to those observed during certain stages of the normal ontogeny of glands, of which they may be regarded as aberrant, superinduced repetitions.

Malignant tumours increase by the continuous growth and proliferation of their constituent cellular elements; and the indications revealed by a thorough study of the minute anatomy of these cells do but strengthen the foregoing conclusions. Biologists have taught us the important part played by the nucleus, in the growth and multiplication of cells. In this connexion it is significant that the nuclei of the cells of malignant tumours are, as a rule, larger and richer in chromatin, and they more frequently originate mitoses, especially asymmetrical and pluripolar forms, than their physiological prototypes. Moreover, it has lately been shown that the "heterotype" mitosis, which is believed to be characteristic of gamic reproductive cells, is also a special feature in the multiplication of the cells of malignant tumours; but of this more anon. These deviations from the normal are but the morphological expressions of a high degree of proliferative activity, which is, indeed, the essential characteristic of the cells of malignant tumours, and the source of all their special qualities. Thus the vegetative activity of cancer cells predominates over all their other functions; and it is in this special dynamic quality that the essence of malignancy concentres. Just as cells embedded in the stroma of an ovarium become ova by excessive growth, at the expense of adjacent X nutritive materials, which they divert from other cells; so we may infer that those cells which originate malignant neoplasms become different from their non-malignant congeners in a similar way.

### The Terms "Cancer," "Epithelioma" (vel Carcinoma), and "Sarcoma."

At the present time the term "cancer" is used in such different senses, that it is necessary for those who employ it to state precisely what they mean by it. In the popular sense every malignant tumour is a "cancer"; but in medical science the term has hitherto usually been restricted to certain malignant tumours—viz., to those of epithelial origin, for which the scientific equivalent, according to the accepted system of nomenclature, should be epithelioma.[1]

Owing, however, to the vogue which the term cancer has obtained in the vernacular, as the synonym of malignant tumour, and to its employment in this sense by the official registrars and statisticians of all modern communities, it seems now impossible to attach to this term any other significance than that sanctioned by popular usage, and this is the sense in which I employ it.

We are indebted to J. Müller for the fundamental conceptions on which the current nomenclature of tumours is based. He first enunciated the important principle, that the structural elements of every tumour have their analogues in the embryonic or adult tissues of the normal organism. In accordance with these ideas, the different kinds of tumours have been designated by adding the quasi-Greek radical *ὤμα* to the name of the corresponding normal tissues whence they originate.

Curiously enough, however, in discriminating the two chief varieties of malignant tumours, this method has seldom been rigidly adhered to; thus malignant tumours of epithelial origin have been commonly designated "carcinoma," and those of connective-tissue origin "sarcoma."

Etymologically the former term simply means crab-like tumour (*καρκίνος*), for which latter the Latin equivalent is cancer. The ancients were much struck by the crab-like aspect of these tumours, but whether this fancied resemblance was the outcome of superficial observation, or of profound study of the disease by dissection, it is not quite clear.[2] Probably, however, they knew more of its nature and its "roots," than we commonly credit them with. At any rate, the term "carcinoma" has persisted in scientific circles, to the exclusion of its more appropriate rival "epithelioma."

In like manner the term "sarcoma" is also exceptionally derived. This is an ancient designation formerly applied to flesh-like tumours (*σάρξ*). Thus Galen says: "We call sarcoma a fleshy excrescence *præter naturam*." There was naturally much diversity of opinion as to just what should be discriminated as flesh—hence the term was at first vaguely used (*tumores carnosi* etc.). Prior to the discovery of the cell theory, it was commonly

[1] For this conception as to the origin of the disease we are indebted to Waldeyer (1867) and Thiersch, the older doctrine as to the connective-tissue origin of malignant epithelial tumours by metaplasia, having been generally abandoned.

[2] Galen says: "In the breasts we often find a tumour in size and shape closely resembling the animal known as a crab, for as in the latter the limbs protrude from either side, so in the tumour the swollen veins radiate from its edges and give a perfect picture of the crab."

employed as synonymous with "fungus." Virchow is mainly responsible for the rehabilitation of the term, and for its modern significance. He described as sarcomata new formations of the connective-tissue type, distinguishable from the corresponding fully evolved tissues by their immaturity. Subsequently they were defined as tumours of embryonic connective tissue, or of some of the modifications that this structure undergoes in evolving the fully developed tissues.

# CHAPTER II

## GEOGRAPHICAL DISTRIBUTION AND INCIDENCE

### Preliminary Aperçu.

At the commencement of the twentieth century the great problem of the causation of tumours, like a gigantic sphinx, looms large on the medical horizon. Of this problem the genesis of cancer is but a part, although a large one. Moreover, it is important to recollect that these growths are not peculiar to mankind, nor even to animals; for, as I have elsewhere shown,[1] similar formations affect trees and other vegetable organisms. Indeed, it seems clear, as I long ago pointed out, that tumours may arise, under certain conditions, in any multicellular animal or vegetable being.

Another important consideration is, that these abnormalities rarely arise in organisms living in a state of nature. It is almost exclusively among domesticated varieties, among those that have been kept long in confinement, or that have been otherwise abnormally circumstanced, that tumours are met with. Savages and wild animals are very rarely thus affected; and it is worth noting that this comparative immunity is very marked throughout the whole of the monkey tribe.

In a general way, it may be said that the animal world is much less prone to malignant and other tumours than humanity; and this appears to me to be due to the fact that animals have been much less extensively subjected to the artificial influence of domestication, and to such other abnormal conditions of existence as I have above referred to, than mankind. At any rate, it is remarkable that nearly all the examples of animal tumours hitherto reported, malignant and otherwise, have been met with in our common domesticated species; and it is significant that the dog is the animal most frequently affected.

Hitherto progress has been hindered by the want of clear conception as to the nature and affinities of the morbid process. Tumour formation has too commonly been regarded as an isolated pathological entity, having no connexion with other biological processes. Yet between tumour formation and morphological variation in general there is, I believe, real affinity; and in ultimate analysis both may be regarded as the outcome of the cumulative effects of changed conditions of existence. Of these conditions the most important seem to me to be changed environment and excess of food.

[1] "The Principles of Cancer and Tumour Formation," London, 1888, p. 85 *et seq.*; also "Vegetable Tumours in Relation to Bud Formation," Trans. Path. Soc. London, vol. xxxviii., 1887, p. 460, and *ibid.*, vol. xl., p. 446. *Vide* also Chapter VI. of this work.

As I have indicated in my work on the "Principles of Cancer and Tumour Formation," it is my belief that factors of this kind play a leading part in the causation of malignant and non-malignant tumours. Now that the fury of the microbic prepossession has somewhat abated, it is to be hoped that these neglected biological factors will receive their due recognition. Changed food, changed habits, and changed environment are as potent factors in pathogenesis, when they tend in this direction, as they are in physiological evolution.

Malignant tumours in mankind and animals consist mainly of albuminous or proteid substances; and it seems not unreasonable to suppose that they may be the outcome of excess of these substances in the body, and especially of such of them as serve for nuclear pabulum. When excessive quantities of such highly stimulating forms of nutriment are ingested, by beings whose cellular metabolism is defective, I believe there may thus be excited in those parts of the body where vital processes are most active, such excessive and disorderly proliferation as may eventuate in cancer. However this may be, I am persuaded that the ascertained facts justify the belief, that there is a certain relation between the conditions of existence—in which alimentation plays an important part—and the incidence of cancer.

**Some Generalities as to the Distribution of Cancer among Mankind.**

In taking a comprehensive survey of the incidence of malignant tumours as they affect mankind, it is important to note the wide range of these maladies, which are practically ubiquitous.

Another striking feature in this connexion, is their much greater prevalence in some localities than in others. Careful study of these inequalities—which although persistent are not permanent—has convinced me that they are due to diversities in the conditions of existence of the respective populations, as I shall subsequently have occasion to demonstrate.

Those who have travelled among savage peoples are practically unanimous in asserting, that malignant tumours are very rarely met with under these circumstances; but in most modern civilized communities diseases of this type are very prevalent. The reputed rarity of cancer among uncivilized people is fully borne out by the reports of the medical officers, missionaries, and other officials who have resided among such populations in various parts of the world, as recorded in official and other reports, to which I shall have to refer more in detail in the sequel. There seems to me to be no warrant for Dr. Bashford's contention, that the civilized and the savage are equally liable, and that the differences above indicated are merely apparent.

To my mind it has been clearly established, that cancer is of most frequent occurrence among the well-to-do, highly nourished communities of occidental Europe; and, within the limits of these communities, as I have proved, the disease is commonest among the well-to-do groups.

Now, if I were asked to state briefly, the chief physical difference between savage and civilized man, I should unhesitatingly reply that it consisted in the latter being much the better nourished; and this is the conclusion of most of those who have travelled among savages. The food-supply of the latter is, indeed, generally irregular and precarious—occasional gluts alternating with long spells of enforced abstinence—and the food they get is badly cooked; whereas the former have constantly available an abundance of highly nutritious and well-cooked food.

Thus, speaking of the natives of the Gaboon region of Equatorial Africa, Du Chaillu says: "No wonder they are so fond of meat: they have it so seldom—*i.e.*, only when they can get it by hunting."

From indications of this kind, it may be inferred that nutrition and alimentation play an important part in cancer causation, as I shall subsequently have occasion to demonstrate more in detail.

It has been noted in the United States, in Australia, and in some other communities, that immigrants are very much more liable to malignant disease than are the native-born population; and that they experience in their new homes higher cancer death-rates than prevail in their native countries. Hence it may be inferred, as I shall indicate more fully in the sequel, that abrupt change of environment may also be a factor in the causation of this disease.

### Race, Complexion, and Conditions of Existence.

In human beings, well-marked constitutional peculiarities and morbid proclivities, are often reputed to be correlated with race and complexion. I now propose to inquire whether the incidence of cancer is influenced by factors of this kind.

So far as present indications go, it appears that all racial varieties of mankind are liable to malignant tumours; but I am not aware of any really satisfactory data, as to the relative incidence of the disease among the different races. From such information as is available, I have come to the conclusion that ethnological factors *per se* are of far less importance in determining the incidence of cancer, than are the conditions of existence to which the race has been exposed. I have arrived at this conclusion mainly from studying the incidence of the disease, as it has affected such well-marked racial types as negroes, North American Indians, and Jews.

In their native African homes, the ancestors of the negro slaves of the United States—like other similarly situated savages—are believed to have been almost exempt from malignant tumours. Most of the early writers testify as to this comparative immunity, which is in entire accord with what we now know as to the present condition of the kindred tribes in Africa, among whom cancer is very rare, as I shall subsequently have occasion to indicate in detail.

Now, in Du Chaillu's interesting "Travels in Equatorial Africa," we have an admirable account of the *modus vivendi* of these tribes, before contact with Europeans, to the salient features of which I have previously alluded as determining this immunity.

Transplanted to the United States, and having lived there in slavery for over two centuries, these negroes were then found by the United States authorities to have acquired greatly increased liability to cancer, to which, however, they were very much less prone than their white masters. Thus, Chisholm's statistics show that, before the emancipation, the whites were more than twice as liable as the blacks, and this was specially noticeable with regard to uterine cancer. The regimen under which they lived during this period, has been well described by Dr. S. Harris [1] as follows: The planters gave their slaves the best hygienic surroundings possible; they had plenty of simple, nutritious, and well-prepared food, and enough out-of-door labour; sleep and recreation were well regulated and sufficient; they were well clothed, forced to keep clean, comfortably housed, and well cared for in sickness. The defective and unhealthy were debarred from reproduction, in which the healthy and able-bodied were encouraged; in short, everything was done to promote health, vigour, and long life; and under this system the slaves multiplied, and had splendid health—better, in fact, than that of their white masters. Thus, the Charleston statistics, from 1822 to the outbreak of the Civil War, show that the general death-rate for whites was 25·98 per 1,000 living, while that for blacks was only 24·04, and throughout the South similar conditions prevailed.

After thirty-five years of freedom, the negroes' health is found to have markedly deteriorated; they now experience an increased general mortality, with greater proclivity to nearly all kinds of disease, especially to tubercle, pneumonia, etc. Even their reputed comparative immunity from malaria has been lost, for the negro death-rate from this cause now greatly exceeds that of the whites. Everywhere, at all ages and in both sexes, these negroes now have greater mortality and morbidity than their white compatriots; and they have become a short-lived race. Thus, the Charleston data show that from 1865 to 1894 (*i.e.*, after emancipation) the negro general death-rate per 1,000 was 43·29, against only 22·7 for the whites.[2]

factor of whites inter-marriage

During the emancipation period, the proclivity to malignant tumours greatly increased among negroes, the mortality returns for 1900, showing a death-rate from this cause of 48 per 100,000 living, as against 66·7 for whites.[3] The Louisville City Hospital reports, and the data collected by Matas for New Orleans, which there are good reasons for regarding as more reliable, in reference to this particular, than the national statistics, show that malignant tumours are now as common there in negroes as in whites (Rodman). With regard to uterine cancer, negresses are now more prone to it than their white sisters, the respective death-rates for 1900, being 20 for blacks and only 15·7 for whites.

Mammary cancer is also now nearly as common in negresses as in white women, the respective death-rates for 1900, being 7·9 for the former and 9·1 for the latter. Thus, from a condition of comparative immunity, these negroes have now become nearly as prone to malignant tumours as

[1] *American Medicine*, September 7, 1901, p. 375.

[2] The Twelfth United States Census Report for 1900, gives the death-rates for negroes and whites, as 31·8 and 17·3 respectively.

[3] The corresponding figures for 1890 are—blacks 36·65, whites 53·93; and, for 1880, blacks 12·17, whites 27·96.

their white neighbours. This result I ascribe to sudden, violent alteration in their mode of life, with its predominant gluttony and laziness.

In like manner, the North American Indians are believed to have been almost exempt from cancer in their primitive savage condition ; but, with the altered mode of life consequent on contact with modern civilization, this comparative immunity has now to a large extent passed away, although they are still less prone to malignant tumours than their white compatriots.

In this connexion it should be borne in mind, that in their primitive condition these savages had no horses and no firearms ; consequently it was no easy matter for them to kill the fleet buffaloes, on which they mainly depended for subsistence ; hence, in their primitive condition, they were generally less well nourished than when, after contact with whites, they had, by the acquirement of horses and firearms, become assured of a constant supply of their favourite food.

In comparatively recent times much valuable information has been forthcoming as to the incidence of disease among Jews, the general outcome of which is to show that this race has a low death-rate, and more than average longevity.

Jews suffer less than most races from tuberculous disease (especially phthisis), pneumonia, alcoholism, diarrhœal affections, and some other maladies ; but they are more prone to diseases of the nervous system, especially to diabetes and insanity.

The Jewish race being widely scattered throughout the world, and the conditions of existence of its various communities being exceedingly diverse, is admirably circumstanced for illustrating the comparative importance of race factors *versus* conditions of existence, in determining the incidence of cancer. Unfortunately, although the comparative pathology of the Jew has been fully worked out for most diseases, with regard to malignant tumours, the data are scanty, and leave much to be desired. On the whole, however, the available indications point clearly to the conclusion, that the liability of Jews to cancer varies with their mode of life, approximating to that of the people among whom they dwell, but generally being somewhat inferior to it. It has often been asserted that persons of the Jewish race are very rarely affected, but this is evidently a mistake. In the United States J. S. Billings[1] found, that the Jewish cancer mortality was about the same as that for the rest of the white population. He gives the cancer mortality per 1,000 deaths as follows :

| | Jews. | Other U.S. Whites. |
|---|---|---|
| Males | 13·58 | 13·09 |
| Females | 21·65 | 23·59 |

Billroth's experience in Vienna was somewhat similar.

Dr. B. W. Richardson, who had considerable experience among the wealthy Jews of West London, found that they were as prone to malignant tumours as other well-to-do people of this part of the metropolis. Referring to the alleged great rarity of this disease among Jews, he says :[2] "I

[1] Tenth United States Census Report for 1880.
[2] *Asclepiad*, vol. viii., 1891, p. 145.

regret to be obliged to state from personal knowledge, that the Jewish community is by no means exempt from cancer. There is no difference in the character of the affection in the Jew, nor any selection of sex, nor any organic selection. With the Jews, as with persons of other races, women are most liable to cancer, but I have witnessed the malady in both sexes. I have known Jewish women who have died of uterine cancer, and of cancer of the breast. My own experience is amply sufficient to disprove the rash assertion of Jewish racial exemption."

An anonymous medical man, who has practised for twenty-five years among London Jews, recently wrote[1] as follows: "There is undoubtedly an impression in the minds of the members of the Jewish community that, far from being exempt, the Jews are especially prone to suffer from malignant growths; and I must admit that I have been somewhat inclined to share this view, although it has sometimes appeared to me that cancer is less prevalent now among them than it was in my earlier experience."

He then gives some statistical data based upon the burial returns of the United Synagogues of London, which for the year 1900, show that 2·3 per cent.[2] of the deaths were stated to be due to cancer, or about one-half the ratio for England and Wales in general.

Comparing this result with the outcome of his own experience, he says: "It is impossible that there is not some fallacy underlying this immense discrepancy"; and he thinks that the explanation of this fallacy is to be found, in the comparatively large number of children and young adults believed to be comprised in the Jewish population, as to which, however, there is no clear evidence.

It appears to me that the author of this instructive communication has failed to find the fallacy, which he believes underlies his statistics. It is hardly likely that such diversities in age distribution as he refers to, will account for such considerable disparities as his data show.

The really important part of the fallacy seems to me to consist in this: that unlike things have been compared together. The great bulk of the London Jewish population, whence these data are derived, is an East-End population, living under conditions of stress and hardship; whereas the average Britisher is a comparatively prosperous and well-to-do being. To get a correct idea of the relative incidence of this disease among Jews and non-Jews, only populations that are, roughly speaking, similarly conditioned should be compared. We see the necessity for this in the fact, that the cancer mortality of West London is so much higher than that of the East End; and this was the case before the present Jewish immigration, when the respective populations consisted almost entirely of Britishers. For instance, during the decennium 1881-1890, the cancer mortality of Stepney was only 3·7 per 10,000 living, as against 5·8 for all England; and at still earlier periods and in other localities, the same disparity is apparent. Even when correction has been made for age and sex distribution, and for deaths in public institutions, this disparity still remains; indeed, in the poorest parts of all our large towns, the cancer

[1] *British Medical Journal*, vol. i., 1902, p. 681; also *ibid.*, vol. ii., 1905, p. 734.
[2] Estimated to be equivalent to a death-rate of 5·2 per 1,000 living, as against 9·5 for London in general (1899).

mortality is always much below the average. Further, in Jewish quarters in London, whether rich or poor, as among non-Jews, the cancer mortality is steadily increasing.

I am indebted to the kind intervention of Dr. F. L. Hoffman, the well-known statistician of the Prudential Insurance Company of America, for the following note on this subject by Dr. M. Fishberg of New York, who has specially studied this subject from the American standpoint. He says:[1] "It appears from all the available data that cancer is by no means rare among Jews, although it is less frequently met with than among non-Jews. This latter condition I explain as due to the fact that cancer of the uterus and female breast is comparatively rare among Jews; and, as is well known, the two last-mentioned organs are the very ones most frequently affected in non-Jews. On the other hand, cancer of the gastro-intestinal tract is very frequent among Jews; thus, nearly 45 per cent. of all cases of malignant disease in Jews occurred in the stomach, intestines, liver, pancreas, rectum etc., while among non-Jews only 23 per cent. of the patients were affected with cancer of these organs. Another point is, that sarcoma is more frequently met with in Jews than in Gentiles."

With regard to these interesting remarks, my own impression is that it has not yet been proved that Jewesses have any special immunity from uterine and mammary cancer; while, as to the gastro-intestinal manifestations of the disease, I have found, as I shall subsequently have to indicate in detail, that more than half of all cancers in Britishers have this localization.

As tending to confirm the belief that Jews generally experience a somewhat lower cancer mortality than their non-Jewish compatriots, reference may be made to an instructive publication by Dr. F. L. Hoffman,[2] in which it is shown that in the United States those of Polish extraction—who are mostly Jews—have a lower death-rate from cancer and tumour, than any other national group in this now composite community.

In illustration of his remarks, he cites the following data, showing the comparative mortality from these diseases of the various nationalities per 100,000 of population:

| Ages. | Native-born United States Whites. | Polish (mostly Jews). | German. | Irish. | Italian. |
|---|---|---|---|---|---|
| 45 to 64 .. | 155·3 | 92·3 | 238·6 | 232·2 | 119·4 |
| 65 and upwards | 374·9 | 263·5 | 561·5 | 479·9 | 392·7 |

Dr. W. A. King, the chief statistician of the Twelfth United States Census Report, referring to this subject, says:[3] "The death-rates per

[1] "Jewish Encyclopædia," vol. iii., p. 529, New York, 1902: to which, however, I have not had access.
[2] "Race and Mortality," *New York Examiner*, October, 1902, p. 635.
[3] Twelfth United States Census Report for 1900, vol. iii., part i.

100,000 of white population, show that the mortality due to malignant tumours was highest among those whose mothers were born in France (92·8), in Scotland (81·8), and in Germany (78·2); and lowest among those whose mothers were born in Russia and Poland (25·7), in Italy (22·8), and in Hungary and Bohemia (31·5). The rate was lower among those whose mothers were born in the United States (48·3), than among those whose mothers were born in Ireland (76·4), or in England and Wales (72·0)."

Here, again, it will be noticed that those of Russian and Polish extraction, who are mainly of Jewish race, have a comparatively low cancer mortality.

In this connexion, however, it must be remembered that these people are among the poorest in the United States; and the Italians, who share their poverty, also share their comparative immunity from cancer.

The lowest cancer death-rates in Austria are met with among the Poles of Galicia and Bukowina, who are largely of Jewish origin; and in the Prussian provinces bordering on Poland, where considerable numbers of Jews are met with, exceptionally low cancer death-rates prevail.

The idea that the eating of pork, *per se*, has anything to do with variations in the incidence of the cancer mortality may certainly be dismissed. From data bearing on this subject, collected by Bauby[1] in the neighbourhood of Toulouse, it is shown that those who eat pork are no more liable to cancer, than those who partake of other kinds of flesh food.

The anonymous correspondent to whose publication I have previously referred, also comes to this conclusion. He says: " At the present time a considerable number of London Jews are by no means strict adherents to the dietary laws, and it will be within the experience of every one who has practised among them, that cancer attacks the orthodox in this respect, as it does the heterodox."

As a general rule, I think it will be found that the Jewish cancer mortality has very little to do with race or with racial customs *per se*; but that it varies, according to the conditions of existence, in different localities and countries.

It should, however, be borne in mind that the Jewish race is of oriental origin; and even now Jews retain something of the oriental heritage of abstemiousness in flesh-feeding, as compared with the grossness in this respect of most of their occidental compatriots.

Many similar facts might be adduced, showing the tendency of the cancer mortality to vary in accordance with the mode of life of individuals, rather than with inherent racial peculiarities.

The United States census reports for several decades, as previously mentioned, have furnished data showing the comparative cancer mortality of each of the chief racial factors contributing to its composite population. These records show remarkable differences between the cancer proclivity of American-born persons, and those whose mothers were born in some other country. Lyon[2] found that the cancer mortality of the

[1] *Bulletin Méd.*, October 14, 1894.
[2] *American Journ. Med. Science*, vol. xxviii., 1901, p. 640.

foreign-born inhabitants of the city of Buffalo (1880 to 1899) was more than 4½ times greater, than that of the American-born inhabitants. In Australia and New Zealand similar occurrences have been noted, as I shall subsequently have occasion to indicate. Of like import is the converse fact, that persons of British descent who have been settled for some generations in the United States, Australia, and New Zealand, then experience a much lower cancer mortality than is prevalent in their original homes.

Dr. J. Beddoe [1] has called attention to the further fact, that although cancer is very prevalent in Norway and Sweden [2]—among one of the blondest populations in the world, comprising less than 5 per cent. of the dark type—it is of the greatest rarity in Iceland and the Faroe Islands, which are inhabited by persons of the same race as the Norwegians.

According to Panum, who wrote more than a quarter of a century ago, cancer was then almost unknown in the Faroe Isles ; and in Iceland it was exceedingly rare, the death-rate from this cause then being only 7 per 100,000 (Hirst).

Dr. R. Jeaffreson, who visited these islands in 1892, informed me that cancer was then very rare there. During some months' residence in the Faroe Isles he never saw a single case, but the resident doctors told him that they occasionally met with an instance—generally in half-breeds or Danish immigrants. In Iceland he found that cancer was as exceptional as in the Faroes. According to Dr. Lazarus-Barlow,[3] however, the disease has much increased of late, the cancer death-rate for 1900, being estimated at 28·8 per 100,000.

In 1890, there were only two deaths from cancer in the whole of Iceland; but in 1900, twenty-two of such deaths were notified.

In Greenland, according to Panum, malignant tumours are of great rarity.

All these facts, which might easily be multiplied, point clearly to the conclusion, that it is neither race nor complexion alone, but rather diversity in the conditions of existence, which determines the incidence of this malady.

The Scandinavian and North European populations are mainly blonde, and they have a very high cancer mortality. The Italians and South Europeans are predominantly dark (70 per cent.), and their cancer mortality is much below the average.

In this country, however, I have convinced myself that the majority of cancer patients are of the dark type; and it is to the female sex that this preponderance is chiefly due. Thus, of 256 female cancer patients examined by me, 150 were of dark and 106 of fair type. In order to appreciate the significance of these results, it must be borne in mind that among the London lower classes, whence these patients were derived, the fair type decidedly predominates, Dr. Beddoe's estimate being 57 per cent. of the latter, to 43 per cent. of the former.[4] On this basis, I calculate

[1] Allbutt's "System of Medicine," vol. i., 1896, p. 35.
[2] In 1900 the cancer death-rate per 100,000 inhabitants was 92.
[3] *Arch. Middlesex Hosp.*, vol. v., 1905, p. 275.
[4] "The Races of Britain," 1885.

that malignant tumours are more than twice as frequent in dark as in fair-complexioned individuals. Here mention may be made of the curious fact that I have never met with, and cannot cite, a single instance of, malignant disease in an albino.

In this connexion it may also be noted, that the stress of life in large towns seems to exert a much more injurious influence on the fair-complexioned, especially in early life, than on those of darker hue. Owing to this cause, it is believed that fair-complexioned types are gradually being supplanted in our large towns. Changes of this kind, which are very subtle and far-reaching, may be among the factors contributing to the increased cancer mortality of modern times.

Finally, it may be here mentioned that among the natives of India, Egypt, Algeria, Australia, New Zealand, South Africa, Canada [1] etc., malignant tumours are extremely rare ; whereas, among the white people settled in these localities, tumours of this kind are comparatively common. Taken in conjunction with the foregoing considerations, this indication evidently points to something in the mode of living, as being the determining ætiological factor in cancer genesis.

### General Survey of the World-wide Distribution of Cancer.

In every part of the world the incidence of cancer presents many variations. Thus, it is much more prevalent in some countries than in others; and within the limits of particular communities—even in the smallest administrative areas—variations of this kind are everywhere noticeable.

I have previously pointed out the much greater frequency of the disease in civilized than in savage communities.

As a general rule, malignant tumours are of much commoner occurrence in temperate and cold, than in tropical or hot regions.

The Danish Government report that cancer is not unknown, even in the Arctic regions ; but no definite information is available as to its incidence. As we get to know more about remote localities, it will probably be found that no settled community is really exempt.

Although it is improbable that any tropical community is really immune from malignant tumours, I am convinced that this type of disease is of very much rarer occurrence among tropical people, than among the inhabitants of the temperate regions, and especially those of occidental Europe.

I shall subsequently adduce abundant evidence from many parts of the world, as to the correctness of this conclusion. Here I can only offer a few remarks on the general aspect of the question. At the outset, it must be mentioned that, with the exception of India and Brazil, all the chief centres of civilization are situated in the temperate or extra-tropical regions—*e.g.*, Europe, China, Japan, United States, British North America, Australia, New Zealand, Cape Colony etc.

In *Europe*, cancer is very much more prevalent than in any of the

[1] Formerly also among the Redskins—now nearly extinct—of the United States.

great divisions of the world; indeed, it is probable that, with the exception of China, more deaths occur from this cause in Europe and the United States, than in all the rest of the world together. Moreover, it is noticeable that the lowest European cancer death-rates are found along its extreme southern fringe—*i.e.*, the shores of the Mediterranean,[1] comprising the Spanish, Italian, Austrian, Turkish, and Grecian littorals, as well as the adjacent islands (Sardinia, Sicily, Corsica etc.).

Although we have no statistical data as to the prevalence of cancer in *Asia*, at all comparable with the comprehensive reports issued by most European Governments, yet, from such information as is available, it is evident that this disease is of much commoner occurrence in the great extra-tropical empires of China and Japan, than it is in the essentially tropical community of India. With regard to Northern Asia, no information is at present available.

In *Australasia* cancer is everywhere fairly common among those of white descent, who are congregated in the extra-tropical regions; but, among the aborigines, it is so rare as to be almost unknown.

It seems perfectly clear that malignant tumours are of much rarer occurrence in *Africa*, than in any other of the great divisions of the world; and most of this vast continent is tropical, with the exception of Cape Colony and its vicinity. It is only in this extra-tropical region that cancer is at all common; and even here, it is those of white descent who are the chief sufferers, for the natives are seldom affected.

In the *American Continent* cancer is much more frequent in its northern or temperate part than elsewhere. Thus, this malady is common in all parts of British North America, except among the aborigines. It is the same in the United States, where, moreover, the cancer mortality of the Northern States is more than double that of the Southern ones.

In Mexico and the Central American communities, cancer is decidedly rarer than in the United States. According to Jourdanet, it is almost unknown in the hot regions of Mexico; whereas in the cool regions, on the high plateaux, it is frequent.

In the tropical regions of South America, of which Brazil is the great exemplar, cancer is rarer than in any other part of the American Continent; and in Brazil, according to Sodré, the malady is rarest in the equatorial regions, increasing in frequency with remoteness from the equator. It accords with this, that cancer is much more frequent in the Argentine Republic and in Uruguay, than in Brazil.

How is the much greater prevalence of malignant tumours in temperate than in hot climates, which this world-wide survey reveals, to be accounted for? Races, says Hippocrates, "are the daughters of climates"; but, as I have previously shown, diversities of this kind cannot be explained by racial peculiarities. The influence of climate *per se*, is as impotent as race *per se*, to solve this problem. Thus, it is only in the conditions of existence, that an adequate solution can be

[1] According to Deniker, the Mediterranean littoral—from Gibraltar to the Tiber—is occupied by one of the six main racial types, of which he believes the present population of Europe is composed; this littoral race is very dark, moderately long-headed, and fairly tall.

found; and in this connexion climate is no doubt a powerful factor. Thus regarded, the greater variability of the temperate as compared with the tropical climates, is probably quite as important as the lower average range of temperature. The greater bulk, muscularity, activity, and superior physical endowment of the people of temperate climates, as compared with their tropical counterparts, may be mainly ascribed to the former cause, which favours more active tissue changes; and so creates the desire for a highly stimulating and nutritious diet, which finds its expressions in a predominantly carnivorous alimentation. On the other hand, tropical people, with their less variable climates, are remarkable for their extreme frugality in living, their open-air existence, and their predominantly vegetarian diet. It is a remarkable fact, but nearly all tropical people manifest decided aversion for a too carnivorous diet; and this cannot be ascribed to backward civilization, but it is rather due to recognition of the fact, that much animal food, in hot climates, predisposes to ill-health and disease. The great precocity of growth and development in tropical populations, with the correlated premature senility, the high general and infantile mortality—which greatly exceeds that of Europe, often to the extent of being more than double—and the consequent short duration of life: all of these effects are probably chiefly consequent on a high range of temperature; while to this factor may also be ascribed the early sexual maturity, and the great reproductive activity which is so noticeable.

Such is the direction in which, as it seems to me, the answer to our question must be sought.

"How vast," says Sir R. Giffen, "must be the economic gulf separating the people of Great Britain from India and like parts of the Empire, when we find that 42,000,000 of people in the United Kingdom consumed in food and drink alone, an amount equal to the whole income of over 300,000,000 of people in India."

In the same strain Meredith Townsend, one of the latest and best exponents of Indian life, writes: "There is no abstemiousness in the world, and no thrift, like the thrift and the abstemiousness of the average native of India. . . . Millions of men in India, especially on the richer soils and in the rice deltas, live, marry, and rear healthy children upon an income which, even when the wife works, is rarely above two shillings a week, and frequently sinks to eighteenpence."

The natives of India live on millet or rice, a little milk, with the butter from the milk, and the vegetables they grow; and of these they partake sparingly. They seldom eat any meat. It is only the Brahmins, the priestly caste, who form but a small fraction of the immense Hindoo population, who never eat any flesh food. The immense majority of the people live a rural life, depending upon agriculture for their subsistence. Such are the conditions of existence in India; and India is typical of the tropics.

Now contrast the tropical mode of living with that prevalent in our country, where all the conditions are so different; where the average wage of the worker amounts to thirty-eight shillings a week; and where the alimentation comprises a meat consumption of over 130 pounds per head per year, together with an abundance of other highly nutritive proteid food products, fats etc.

Moreover, it is in the tropics that the human race is believed to have originated, and there the anthropoid apes, our nearest animal connexions, who are mainly vegetarians, still flourish ; and are seldom, if ever, affected with malignant tumours.

It is to conditions such as these and their consequences, as I shall often have occasion to point out in the sequel, that the greater prevalence of malignant tumours in temperate, than in tropical countries, must be ascribed.

Unlike certain specific infective diseases, such as malaria, with which cancer has often been compared, this malady is not limited to definite localities, but is practically ubiquitous. Ubiquity differentiates cancer from all parasitic maladies, for even tubercle is far less ubiquitous than cancer. Cancer and tubercle centre in temperate climates, whereas malaria is the predominant malady of the tropics.

Tumours—including the malignant kinds—seem to me to be more akin to malformations *per excessum*, than to specific endemic maladies. The congenital origin of many tumours, malignant and otherwise, testifies against their parasitic origin. Malformations and other morphological variations, like tumours, are found in all localities, climates, and races ; and it is specially noticeable that, like tumours, they are much commoner in civilized humanity than in savages; and in domesticated animals, as well as in those that have been kept long in confinement, than in animals accustomed to a less artificial environment. Here it may be mentioned, that the prevalence of defects of this kind has greatly increased in our country during the last half-century.

## General Survey of the Distribution of Cancer in Europe.

Statistical records show that malignant tumours are very much more prevalent in Europe, than in any other of the great divisions of the world ; and it is specially in the northern and central parts of this Continent that the cancer mortality is so terribly high. In Southern Europe the incidence of the disease is much less, and I have previously referred to its special rarity along the Mediterranean littoral.

Although the official reports of different countries are, in some respects, not always strictly comparable, yet the following data may be taken as giving a fairly accurate notion as to the comparative incidence of the disease. The figures show the cancer death-rates per 100,000 living for the year 1900, unless otherwise stated.

The maximum incidence of the disease seems to be in Switzerland, where, according to Nencki, the cancer death-rate for the year 1898 was 132, and for the decennium 1895-1904 it has been estimated at 128.

In Denmark the malady appears to be nearly as rampant as in Switzerland, for the cancer death-rate for all the towns, for the years 1892-1897, averaged 130.

France comes next with a cancer death-rate of 104, for all towns of above 3,000 inhabitants;[1] and is closely followed by Sweden, with a cancer mortality of 102 for its town population.

The figures for the other countries are as follows: Holland, 93; Norway, 92; England and Wales, 82; Scotland, 80; Germany, 71 (Prussia, 59; Bavaria, 98; Baden, 101; Saxony, 95; Wurtemburg, 93); Austria, 70; Ireland, 61; Italy, 52; Spain, 39; Belgium, 36 (1880-1887); and Hungary, 33.

As to Russia, no satisfactory data are available, but the disease seems to be everywhere fairly prevalent.

In Greece, Turkey, and the Balkan countries, cancer is believed to be rare, but hardly any recent information is available;[2] and with regard to Portugal it is the same.

Along the Mediterranean littoral, as previously mentioned, some of the lowest cancer death-rates in Europe are to be found. Thus, on the Spanish coast, the figure for the province of Almeira is 25, that for Valencia 28, for Genoa the same, for Alicante 29, while the figures for Andalusia and Catalonia are equally low. Among the natives at Gibraltar the cancer death-rate is 25, and at Malta the disease is reported to be very rare among the natives.[3] On the French coast, the cancer-mortality is everywhere much below the French average; but precise data are only available for the towns, and of these Marseilles has the lowest cancer death-rate of any large town in France—viz., 69. In Corsica the disease is very rare, the figures for the chief towns being 32 (1895). In Sardinia the cancer death-rate is only 19, and in Sicily 34. On the Italian coast the figure for Calabria, for Basilicata, and for Apulia is 30, and for Abruzzie Molise 35. On the Austrian littoral, the cancer death-rate for Croatia is 16, and for Dalmatia 19.

An examination of this list shows, that malignant tumours are of most frequent occurrence in those communities where the inhabitants are predominantly well-to-do; and where they now are, and for some time have been, exceptionally well nourished. At first sight, it might be thought that such a description hardly applies to the countries at the head of my list, for the aggregate wealth of Switzerland and the Scandinavian countries is comparatively inconsiderable. It must, however, be borne in mind that these communities have no paupers and no millionaires; and a careful examination of the subject reveals the fact that their average of well-being is higher than elsewhere in Europe, as is indicated by their exceptionally low general, infantile, and tuberculous death-rates. In fact, vital statistics show that the inhabitants of these countries are, on the average, the healthiest and best-nourished people in Europe.

Very different conditions of existence prevail where the lowest cancer death-rates are found. Here the people are predominantly poor, of necessity very frugal, subsisting on an alimentation which comprises but little proteid food; and these conditions are chronic.

The attempt to explain these diversities as due to inequalities in the

[1] Comprising only about one-third of the entire population.
[2] For Servia (1895 to 1904) the cancer death-rate has been estimated at 8 per 100,000 living; the phthisis death-rate being 245.
[3] Boudin states that 3,200 deaths among the indigenes (1822-34) comprised not a single cancer death.

age and sex distribution of the respective populations has completely failed, wherever the requisite data for making such corrections have been available; and, *primâ facie*, it is obvious that such diversities as those above indicated, are far too marked to be explained in this way.

Here it may be noted that the people of Europe now are, and for a long time have been, on the average, better nourished than those of any of the other great divisions of the world.

In plenty the *Hydra* buds, in less favourable circumstances it reproduces sexually. Mankind, under similar circumstances, as I have indicated in my work on the "Principles of Cancer and Tumour Formation," is apt to be affected in an analogous way. Here the gemmation manifests itself as tumour formation, which may be regarded as reversion from dominant sexuality, to a more or less incomplete attempt at agamogenesis. In ultimate analysis, then, both gemmation and tumour formation may be ascribed to what Geddes calls predominant anabolism. The more thoroughly the cancer problem is studied in its ensemble, the more manifest this inter-relation becomes.

The following remarkable data by Bertillon, showing the comparative fertility of the well nourished and of the poorly nourished, is of much interest in this connexion :

TABLE SHOWING BIRTHS PER 1,000 WOMEN—AGED 15 TO 50—PER ANNUM, IN DIFFERENT QUARTERS OF LONDON, PARIS, BERLIN, AND VIENNA.

| Classes of Population. | Average. | London. | Paris. | Berlin. | Vienna. |
|---|---|---|---|---|---|
| Very poor .. .. | 153 | 147 | 108 | 157 | 200 |
| Poor .. .. .. | 132 | 140 | 95 | 129 | 164 |
| Comfortable .. .. | 112 | 107 | 72 | 114 | 155 |
| Very comfortable .. | 105 | 107 | 65 | 96 | 153 |
| Rich .. .. .. | 78 | 87 | 53 | 63 | 107 |
| Very rich .. .. .. | 51 | 63 | 34 | 47 | 71 |

This antagonism between individuation and reproduction long ago secured recognition in the homely adage, "The rich for luck, and the poor for children"; and in this connexion Adam Smith called attention to the poor half-starved Highland crofter women, with their families of twenty or more children.

I shall often have occasion to refer to these fundamental etiological conceptions in the sequel, but for the present these brief introductory remarks must suffice.

It accords with the foregoing that the cancer mortality of the capital cities and great towns, where the wealth of the nations is clotted, is generally above the average; while in rural districts the disease is less prevalent than in towns, although there are here some exceptions. There can be no doubt that the town people, owing to their greater earning capacity, are, as a rule, better nourished than the rural inhabitants; although the great inequalities in the distribution of wealth, which are specially prevalent in urban communities, with their paupers and millionaires, often neutralize this effect.

The cancer death-rates for the chief European capitals for 1900, were as follows: Copenhagen, 139; Stuttgart, 127; Dresden, 125; Vienna,[1] 121; Munich, 119; Edinburgh, 116; Stockholm, 110; Berlin, 109; Paris, 105; Berne, 105 (with canton); St. Petersburg, 100; Amsterdam, 98; London, 96; Dublin, 93 (with county); Prague, 85; Madrid, 78; Rome, 77; Buda-Pest, 72; Christiania,[2] 66; and Brussels, 44.

In Constantinople, Athens, and the capitals of the Balkan States, the disease is said to be comparatively infrequent, but no recent data are available.

For the chief European towns the corresponding rates are as under:

Geneva, 177; Rouen, 173; Lyons, 153; Florence, 137; Reims, 132 (1895); Danzig, 122 (1895); Ravenna, 120 (1887-1899); Strassburg, 118; Keil, 113; Halle, 112; chief Danish towns, 111; Breslau, 109; Dundee, 107; Venice, 103; Milan, 101; Trondhjem, 99; Utrecht, 97; Hamburg, 97 (1898); Bordeaux, 97; Aberdeen, 95; Cologne, 91; Hague, 90; Rotterdam, 90; Birmingham, 85; Seville, 85; Glasgow, 82; Bremen, 81 (1875-1878); Malmö, 80; Manchester, 78; Liverpool, 77; Marseilles, 69; Dusseldorf, 61; Genoa, 59 (1887-1899); Turin, 59 (1887-1899); Naples, 56 (1899); Barcelona, 53; Valencia, 39 etc.

Some of the highest cancer death-rates known to me have been met with in small villages of Normandy—viz., Oulchy, 400; St. Sylvestre,[3] 363 (1880-1887); Rocroi, 266; and Cormeilles, 203. In this part of Normandy cancer is more prevalent than in any other district of France—viz., for the departments of Eure et Loire 167, and for l'Aisne 161 (1900). A very high cancer mortality is also reported at Cracow, 316 (1887-1898); Erlangen, 250; and in the canton of Lucerne, 204 (1898).

With these phenomenally high rates, it is interesting to compare the following exceptionally low ones—viz., Croatia and Sclavonia (provinces of), 16; Valais (canton of), 16 (1898); Shetland Isles, 16 (1874); Cagliari, 18 (1887-1891); Dalmatia (province of), 19; Sardinia, 19; Ajaccio, 19; Corti, 20; Oviedo (province), 21; Kerry (county), 27 etc.

It has long been a moot question whether malignant tumours are of more frequent occurrence in urban or in rural districts; and even in modern times, with the aid of statistical data, the answers given to this question are not always unanimous.

Unfortunately, the English national statistics, so excellent in most respects, contain no data bearing directly on this important subject; but, from such crude information as can be indirectly gleaned, it appears that at the present time the disease is as frequent in the rural districts as in the towns.

As long ago as 1838, William Farr investigated this subject, and found that the cancer deaths in the rural districts were, to those in the towns, in the ratio of 1 to 0·97. Walshe soon afterwards, basing his calculation on information contained in the Registrar-General's reports for the years 1838-1841 (which comprised the metropolis and twenty-five towns on the one hand, and a number of rural districts on the other), found that the cancer mortality in the rural districts then was 19·8 per 100,000 living, and in the towns 18·3.

[1] Exclusive of sarcoma. [2] And district. [3] Population 379.

When these estimates were made, 65 per cent. of the population lived in the country. Now, however, such has been the rapid increase of urbanization, only 23 per cent. of the population dwell in the country, and of these a large proportion really belong to the towns in whose suburbs or vicinity they reside. Indeed, so thoroughly urbanized is the country at the present time, that differential vital statistics as between town and country have lost much of their significance.

Tatham has investigated this subject, on the basis of the statistical data for the year 1901. He found that, at ages above thirty-five, the crude and corrected (for sex) cancer mortality per 100,000 living, in urban and rural districts, was as follows :

| | Crude Rate. | Corrected Rate. |
|---|---|---|
| Urban | 246 | 260 |
| Rural | 268 | 234 |

In Scotland, where for many years the national statistics have been kept in such a way as to facilitate comparisons of this kind, cancer is more prevalent in the towns than in the country ; but the distinctions are not very marked, probably because the Scotch people, like the English, have been so completely urbanized—over 75 per cent. of them being massed in the towns—that few parts of the country are exempt from urbanizing influences. Cancer is least prevalent in the islands, where the conditions are purely rural, the people are poor, and the alimentation is mainly vegetarian.

The following figures showing the cancer death-rates illustrate this :

| | 1905. | 1900. | 1891. | 1888. |
|---|---|---|---|---|
| Principal towns | 92 | 84 | 70 | 63 |
| Large towns | 80 | 70 | 67 | 60 |
| Small towns | 79 | 77 | 61 | 59 |
| Midland rural districts | 99 | 83 | 70 | 61 |
| Insular rural districts | 79 | 56 | 61 | 58 |
| Average for all Scotland | 89 | 81 | 68 | 61 |

Ireland is the least urbanized and poorest part of the United Kingdom, and it accords with the foregoing indications that it is also the least prone to cancer ; and when the corresponding cancer death-rates have been corrected for diversities in age and sex distribution, this comparative immunity is seen to be even more marked than it at first appeared to be.

The highest Irish cancer mortality is met with in well-to-do Ulster, which comprises the large city of Belfast, where the population is largely of Scotch descent and of Scotch habits ; but the rural division of Armagh has the highest cancer death-rate—viz., 104 (1897-1901). Next in order come the counties of Dublin (84) and Londonderry (82), each comprising a large town ; while the lowest rates are in the wild and poverty-stricken West—in Kerry (26), Mayo (36), and Clare (38), the figures being for the period 1897-1901.

The French statistics[1] illustrate similar conditions in a very striking way, although they give no information for the rural districts, except as

[1] For several official publications relating to this matter, I am indebted to M. le Dr. J. Bertillon, Chef des travaux statistiques de la ville de Paris ; and to M. Monod, Directeur de l'Assistance et de l'hygiène publiques, to both of whom I tender my thanks.

to the small towns known as *chefs-lieux d'arrondissement*. Thus, for the years 1895 and 1900, the figures were as follows :

| | 1895. | 1900. |
|---|---|---|
| Paris | 119 | 121 |
| All towns of above 100,000 inhabitants | 108 | 112 |
| All towns of from 100,000 to 30,000 | 96 | 99 |
| All towns of from 30,000 to 20,000 inhabitants | 92 | 95 |
| All towns of from 20,000 to 10,000 | 94 | 91 |
| All towns of from 10,000 to 5,000 | 73 | 74 |
| Chefs-lieux d'arrondissement of under 5,000 inhabitants | 68 | 82 |

For Prussia, Laspeyres[1] has given the following table, which is based on the official returns for the period 1891-1895 :

| | Males. | Females. |
|---|---|---|
| Large towns | 63 | 97 |
| Medium-sized towns | 63 | 83 |
| Small towns | 53 | 63 |
| Towns in general | 62 | 79 |
| Rural districts in general | 35 | 36 |
| Prussia (average for whole) | 46 | 53 |

In Austria, the cancer mortality for the towns presents a similar gradation (Kolb).

For the towns of Bavaria, the cancer death-rate is 120, and for the country 80.

For Saxony, the corresponding figures are, for the towns 106, and for the country 89 (Prinzing).

In Norway, the cancer death-rate for the towns, in 1897, was 100; and for the rural districts 80 (Geirsvold).

Of twenty-three Dutch towns of over 20,000 inhabitants (1897-1900), fourteen had a cancer death-rate above the average for the whole country (De Bovis).

These data prove that the inhabitants of towns, and especially of the large towns, are more prone to cancer than those of the small towns and of the rural districts. There are, however, exceptions, as may be gathered from study of the previously cited data. Moreover, in Switzerland, Denmark, Sweden, Norway, Bavaria, and Baden, all of which have very high cancer death-rates, the conditions of existence are predominantly rural; whereas England, Scotland, and Belgium, whose populations are more completely urbanized than those of any other communities, manifest only moderate proclivity to the disease. Among the towns similar occurrences are noticeable—*e.g.*, Geneva, Rouen, Lyons etc., have higher cancer death-rates than Berlin, Paris, or London; the cancer death-rates of Danzig and Keil surpass those of Berlin; while Florence and Ravenna have a greater proclivity to cancer than Rome etc.

If it were possible to correct these various death-rates for diversities of age and sex distribution, for the presence of hospitals and other disturbing factors, some of these anomalies might then be less conspicuous; but, even so, the main indications of the crude data would not be changed. Thus, as Laspeyres has shown, the cancer death-rates of men from sixty to seventy years old, in the large towns of Prussia, amounted to 68; whereas the corresponding figure for the rural districts was only 23·7, and at all other age periods similar differences were noticeable. These

[1] *Central.-Bl. f. allg. Gesundheitspflege*, 1901, S. 342.

differences cannot be explained as the result of presumed better diagnosis by the urban medical practitioners, as I shall subsequently have occasion to prove. Therefore, it seems clear that, in modern communities, urban populations are generally more prone to malignant disease than are the rural inhabitants. In Sweden, however, as in England, it has been noted that the cancer death-rate of the small towns surpasses that of the large ones; which, with other similar indications, seems to show that the incidence of the disease is determined more by the local conditions of existence, than by urbanization or ruralization *per se.*

Here, however, it is necessary to point out a peculiar feature of cancer, wherein it differs from nearly all contagious diseases—viz., that its incidence never shows any proportional variability with mere density of population. This was long ago shown to be the case for our country by Walshe, C. H. Moore, and Haviland. In this respect cancer differs markedly from tubercle.

By comparing the figures showing the density of population in European communities, with those indicating the corresponding cancer death-rates, very striking disparities in this respect are at once revealed. Thus, Belgium and England, with 550 and 540 inhabitants respectively to a square mile, are the most densely populated communities in Europe; but they are far from occupying a similarly exalted position in the cancer list; and, although nearly equal as regards density of population, their proclivity to cancer shows no corresponding similarity. Switzerland and Denmark, which head the cancer list, have only a medium density of population—viz., 197 and 146 per square mile respectively. On the other hand, Norway and Sweden, the most sparsely populated countries in Europe, with less than thirty inhabitants per square mile, have very high cancer death-rates.

This peculiarity in the incidence of cancer tells against contagion, as the causative factor of variations in its distribution; and points rather to diversities in the conditions of existence, and especially to such as are independent of mere density of population.

### General Survey of the Distribution of Cancer in Asia.

All available indications point to the conclusion, that cancer is everywhere much less prevalent in Asia than in Europe.

Nearly all the old writers on the geographical distribution of disease agree in stating, that cancer is more prevalent in China than in any other Asiatic community. With regard to recent sources of information, the mean annual death-rate from cancer in Hong-Kong for the period 1895-1904, was 4·45 per 100,000 inhabitants;[1] while that for England and Wales, during about the same period, was 81.

Of 2,981 Chinese adults admitted in the Tang Wah Hospital at Hong-Kong in 1900,[2] 8 had malignant tumours; and of 3,185 admitted in 1902,[3] 10 were similarly affected: thus, of these 6,166 inmates, 18 had cancer, or 1 in 342.

[1] Report on Cancer in British Colonies, 1906.
[2] Report of the Civil Medical Officer, 1900.
[3] Colonial Report, No. 19, 1902. The Tang Wah Hospital is a kind of refuge where the poorest of the Chinese go when very ill or moribund.

Of 1,299 Asiatics admitted into the Government Civil Hospital at Hong-Kong in 1902, 11 had cancer, or 1 in 118.

In London general hospitals the proportion of inmates affected with cancer has lately been estimated at 1 in 20.

Of the 1,305 deaths of Chinese in Hong-Kong hospitals during the year 1902, only 3 were due to cancer, or 1 in 435.

A few years ago I wrote to Dr. Cantlie, who was then Government surgeon at Hong-Kong, asking him for information on this subject. He very obligingly replied as follows : "I do not think I have been without a case of malignant disease under my care ever since I came to China six years ago." Of 3,608 consecutive Chinese hospital in-patients under his care, 114 had malignant disease, or 1 in 31. Of Cantlie's 114 Chinese cancer patients, the primary seats of the disease were as follows : female breast, 38 ; upper jaw, 25 ; lower jaw, 14 ; penis, 9 ; uterus, 8 ; parotid, 5 ; hip, 5 ; tongue, 4 ; lip, 3 ; and thigh, 3. At Dr. Kerr's hospital in Canton, during the year 1887, 30 cases of malignant tumours were operated on, including 11 amputations of the female breast. Strange to relate, Cantlie has never met with cancer of the stomach among the Chinese. With regard to their diet, he says : "All Chinamen eat fish and pork at morning and evening meals. Fowls and ducks are always on the table of all but the most humble of the coolie class, and they do not have them because they cannot afford them. I hope this will be a sufficient answer to those who maintain that Chinamen live on rice. It is not nearly so true as that the Scotch live on porridge."

In the Hong-Kong district, non-malignant tumours seem to be even rarer among the Chinese than the malignant ones, for of 6,166 hospital inmates, only 8 were thus affected. On the other hand, malarial maladies are very common, and tubercle is prevalent, according to Dr. W. Hunter.

Dr. J. P. Maxwell[1] has lately published some valuable information as to the prevalence of malignant tumours in the province of Fokien, South China, which is situated just outside the tropical zone.

During three and a half years, 11,000 patients were seen at the Chang-poo Hospital; and of these, 54 (males 42, females 12) were subject to these maladies, or 1 in 203. Of the males, 24 suffered from cancer (œsophagus, 7 ; pylorus, 2 ; rodent ulcer of the face, 3 ; penis, 2 ; and 1 each as follows : lip, palate, leg, jaw, tongue, face, scalp, eyelid, thyroid, and groin) ; and 18 from sarcoma (femur—periosteal, 3 ; spindle-celled of connective tissue, 4 ; neck, 5 ; and 1 each in the following situations : antrum, upper jaw, lower jaw, naso-pharynx, testis, and skin of back—melanotic). Of the females, 7 had cancer (breast, 4 ; œsophagus, 1 ; and rodent ulcer of the face, 2) ; and 5 had sarcoma (axilla, 1 ; lymphadenoid, 1 ; upper jaw, 1 ; neck, 1 ; and lung, 1).

The population furnishing these cases lived chiefly on rice, only a small amount of animal food and alcohol being consumed.

According to Dr. Elizabeth Reifsnyder,[2] of Shanghai, cancer of the uterus and breast is common in that part of China, and ovarian cystomata are also often met with.

[1] *Journal of Tropical Medicine*, September, 1904, p. 270.
[2] *American Journal of Obstetrics*, etc., vol. xxxi., 1895, p. 512.

In his interesting "Notes on Surgical Practice among the Natives of Shanghai," Dr. E. Henderson[1] points out that the establishment of mission hospitals, giving gratuitous treatment, has proved that cancerous and sarcomatous tumours are not uncommon among the natives of that vicinity. Non-malignant tumours (lipoma, etc.) of exceptionally large size are also fairly often seen, owing to the inabilityof native practitioners to remove them. He reports cases of fibro-cystic sarcoma of the lower jaw and of the parotid region, under his own observation. Tuberculous, malarial, and syphilitic affections are very rife The staple diet comprises rice and other vegetable products, with fish, pork, or fowl if means permit. Tea is the usual drink, and samshu, a native spirit made from rice, is also freely taken, but hardly ever to such an extent as to cause drunkenness.

According to a recent publication by Dr. Brunet,[2] cancer is comparatively uncommon in those parts of China where the bulk of the people live on an almost exclusively vegetarian diet, being too poor to purchase any of the various flesh foods which are there used for culinary purposes. He points out that the Chinese altogether eschew milk as food, even for infants; and it is a mistake to suppose that the majority of them live on rice, as this staple can only be afforded by families whose means are above the average, most of the population having to be satisfied with cheaper grains, such as millet.

Dr. Gray[3] reports that cases of cancer of the mamma, lip, and penis are often seen at the mission hospitals in North China.

At the hospital for Chinese in Tartar City, Pekin, Dr. Foulkes[4] found that cancer was fairly common. He mentions cases of epithelioma of the lower lip and œsophagus, and spindle-celled sarcoma of the breast in a girl aged seventeen.

In the United States (1900),[5] the 48,565 Chinese (mostly adult males) comprised in the registration area, had a cancer death-rate of 49 per 100,000 living, or about 1 in 40 of the total mortality from all causes. They experienced very heavy mortality from phthisis and pneumonia, but the deaths from malaria were very few. For the white population, the cancer death-rate for all ages and both sexes was 66 (males 50). It would seem, therefore, as if the change of habitat had greatly increased the liability of the Chinese immigrants to malignant disease. A similar occurrence has been noted in Australia, with respect to the Chinese coolie immigrants in Victoria.[6]

Malignant tumours are believed to be less prevalent in *Japan* than in China; however, according to a recent estimate, the Japanese cancer death-rate is placed at 49 per 100,000 living, but on what evidence this figure rests I am unable to say.

It accords with the above-mentioned belief, that the Japanese immi-

[1] *Edinburgh Medical Journal*, vol. xxii., 1876, pp. 405, 690; and vol. xxiii., 1877, p. 118.
[2] *Revue d'Hygiène*, t. xxvii., Nos. 2 and 3, 1905.
[3] *Lancet*, 1901.
[4] *Indian Medical Gazette*, September, 1902, p. 348.
[5] Twelfth Census Report of the United States (1900).
[6] *Lancet*, vol. i., 1904, p. 424; also *Australian Medical Gazette*, September 21, 1902, p. 169.

grants in the United States are less prone to these diseases than the Chinese, their cancer death-rate in 1900, being 24 per 100,000. The Japanese subsist mainly on rice, beans, millet, and other vegetable productions, to which those who can afford it add fish, eggs, small quantities of meat etc. They are of very frugal and temperate habits, andr arely indulge in alcoholic drinks.

In *Korea*, malignant tumours are not common, but most of the chief local varieties have been met with.

Nothing definite is known as to the incidence of these maladies in *Northern Asia* and *Siberia*.

In *Arabia*, *Persia*, and *Asia Minor*, cancer is reported to be rare (Lombard) ; but in the *Caucasus* it is by no means uncommon, especially among Russians and Armenians. In the adjacent province of Astrakhan cancer is moderately prevalent, and tubercle is common (Dallinger). In *Cyprus*,[1] 49 cases of malignant and 100 of non-malignant tumours, were met with among about 30,000 hospital and dispensary patients, during 1903.

In the absence of statistical reports as to the incidence of malignant tumours and other diseases among the immense population of *India*, which in its entirety approximates 350,000,000, all estimates must be regarded as tentative and conjectural. The great extent of the country and its teeming millions make it very difficult, even for those who have been long resident there in a professional capacity, to arrive at correct conclusions. The few hospitals and dispensaries in India draw their patients from immense multitudes and vast areas, so that, although many cases of cancer may be constantly under treatment, the proportionate prevalence of the disease in the general population may be much less than the medical officers of such institutions are apt to believe. After careful study of all available sources of information, it appears to me clearly indicated that malignant tumours are very much less prevalent, *pro rata*, in India than in Europe ; but neither the Hindoos, who number over 200,000,000, nor the Mohammedans, who number over 60,000,000, nor any of the other races of India, can claim exemption.

A recently issued Government Report, based on the percentage of cancer cases to the total number of all diseases treated in the hospitals and dispensaries of the various provinces, gives the following results ; but, for the reasons above stated, the incidence of the disease in the general population is certain to be very much less than in these hospital and dispensary patients, low as this ratio is :

| Provinces. | Proportion of Cancer Cases to 100 of all other Diseases. |
|---|---|
| Punjab | 0·700 |
| Central division | 0·700 |
| Berar | 0·700 |
| Burmah | 0·610 |
| Agra and Oudh | 0·050 |
| Bombay | 0·050 |
| Bengal | 0·025 |
| Madras | 0·024 |
| Assam | 0·005 |

[1] Colonial Report, 1903.

In interpreting these figures, it is necessary to remember that the patients were nearly all adults, the men being three or four times as numerous as the women, who are with difficulty persuaded to avail themselves of hospital treatment.

In a general way, it may be said that all the varieties of malignant tumours met with in Europe have their counterparts in India. My statistics show that in English hospital patients 85·4 per cent. of these growths are epithelial cancer, the remaining 14·6 per cent. being sarcomata. Most Indian statistics, however, reveal a much greater relative proportion of the latter ; indeed, the data from some districts seem to show that sarcomata are nearly as prevalent as carcinomata. A remarkable negative feature of the Indian Reports, is the almost complete absence from them of cases of malignant disease of the stomach (pylorus) ; and an equally noteworthy positive feature, is the unusually great predominance of external cancers.[1] Mammary, uterine, and hepatic cancers, seem to be relatively much less prevalent in India than in England. The extraordinary comparative frequency of some external reputed manifestations of the disease in India, such as " cancer " of the penis and cutaneous system, especially the curious " Kangri-burn cancer," is so unparalleled in European experience, and these lesions seem in other respects so different from epithelial cancer, as it is met with in this country ; that I suspect the majority of them will eventually turn out to be pseudo-malignant lesions due to microbic infection rather than true cancer, as I shall subsequently have occasion to point out more in detail.

The data available do not enable us to determine the comparative sex prevalence of the disease, owing to the great majority of hospital patients being males, the inhabitants of India being very averse to their women entering hospitals.

Some valuable information as to the incidence of malignant disease in the Punjab and at the Mayo Hospital, in Lahore of that province, has lately been published by Dr. D. W. Sutherland.[2] He concludes that cancerous affections are not at all common in this part of India. In all the Punjab hospitals and dispensaries for the years 1899-1903, the yearly average of patients treated for malignant tumours was 266, and the proportion of these tumours to the total cases treated for all diseases was only 0·08 per mille.

At the Mayo Hospital in Lahore, during the decennium 1892-1903, 43,412 in-patients were treated ; and of these, 792 had some form of malignant tumour (carcinoma, 400 ; sarcoma, 334), or 1 in 55. These patients were drawn from the 25,000,000 of the Punjab, every part having contributed, and some even came from adjoining States.

In the population of the Lahore district, Hindoos and Mohammedans are about equally represented, and both races proved to be about equally liable to malignant disease ; but with respect to carcinoma, the Hindoos were eighty cases in excess of the Mohammedans, owing to individuals of

[1] Of 1,589 cases of cancer from India analysed by the Imperial Cancer Research Fund Staff, 1,513 involved the external surface of the body, and only 76 internal organs (Fifth Report, 1907).

[2] *Arch. Middlesex Hosp.*, vol. iii., 1904, p. 84.

their race furnishing seventy-two cases of " cancer " of the penis, whereas there was not a single case of this local variety of the disease among the Mohammedans. The latter practise circumcision, and Sutherland ascribes their immunity from this local form of the disease to this custom. The proportion of cases of carcinoma of the penis in the Hindoos, is so enormously in excess of what is met with in Europe, that I wonder if the diagnosis may not be in fault. Is it quite certain that in most of these cases, we may not have to do with a form of contagious venereal condyloma, to which the well-known libidinous practices of the Hindoos render them specially liable ? [1]

Syphilis and malaria are of great frequency among the populations whence these patients came, but insanity and tubercle are rare. With regard to their diet, both races are mainly vegetarian, taking only a little flesh food on the occasions when they can afford it. Alcoholic drinks are tabooed by the Mohammedans, but the Hindoos indulge freely in them. Nearly half of the total patients were employed in cultivating the soil, much smaller numbers were shop-keepers, general labourers, beggars, etc. The maximum age of prevalence for carcinoma was from forty to fifty (114 cases out of 395)—considerably earlier than in Eruope ; and for sarcoma, of 350 patients, 79 were from thirty to forty years old, 68 from twenty to thirty, 58 from forty to fifty, and 44 from ten to twenty years old.

With regard to the localization of the disease, the most striking fact, next to the frequency of " cancer " of the penis in the Hindoos, is the complete absence of malignant disease of the stomach, of which not a single instance is recorded.

The chief seats of carcinoma in 396 cases (males 270, females 126) were : penis, 72 (all Hindoos) ; skin, 58 ; breast, 50 ; rectum, 30 ; uterus, 23 ; liver, 23 ; tongue, 20 ; lip, cheek, mouth, and palate, 13 ; bladder, 6 ; pharynx, 5 ; larynx, 5 ; anus, 5 ; intestines, 3 ; rodent ulcer, 3 ; pancreas, 3 ; œsophagus, 2 etc.

The chief seats of sarcoma in 334 cases (males 255, females 79) were : head and neck, 112 (jaws, 53 ; face, 13 ; orbit, 13 ; nose, 10 ; naso-pharynx, 9 etc.) ; lower limbs, 59 (thigh, 17 ; leg, 13 ; knee, 9 ; foot, 7 etc.) ; upper limbs, 24 (shoulder, 7 ; arm, 6 ; elbow, 4 ; forearm, 4 ; hand, 3 etc.) ; trunk, 21 (abdomen, 7 ; back, 7 etc.) ; various organs (testis, 8 ; parotid, 5 ; ovary, 3 ; tongue, 2 ; breast, 1 etc.).

In the above, twenty-eight cases of sarcoma of the long bones are comprised.

All the different histological varieties of carcinoma and sarcoma were represented.

In *Kashmir*, a state adjacent to the Punjab, with a population of several millions, malignant and other tumours are, according to Dr. E. F. Neve,[2] not particularly rare for India.

This country is a high-lying valley, surrounded by high mountains, of which extensive tracts are permanently under water, while large areas

[1] Referring to cases of this kind in Egypt, where cancer is phenomenally rare, Dr. Madden says : " Condylomata flourish with truly tropical luxuriance."

[2] *Indian Medical Gazette*, May, 1902, p. 164.

are liable to annual floods. During the summer season the valley is practically an alluvial plain covered with rice-fields and swamps, yet malaria is rare. Phthisis, pleurisy, and pneumonia are also rare, but rheumatic affections are prevalent. The people, who are Hindoos, live mainly on rice, the cultivation of which is their staple employment.

During the decennium 1890-1899, 2,020 natives with tumours were operated on at the Kashmir mission hospitals, more than half of which were malignant.

Of 486 epithelial cancers, the sites were as follows: "Kangri-burn cancer" (skin of abdomen, thigh, or vicinity), 363; female breast, 29; leg, 21; chest, 13; eyelids, 6; lip, 5; head, 5; face, 4; foot, 3; heel, 3; wrist, 3; rectum, 3; eyeball, 3; ear, 3; nose, 2; neck, 2; back, 2; penis, 2 etc. Those attacked were the mature and elderly.

As compared with Sutherland's statistics for the adjacent Punjab, some extraordinary diversities in localization are noticeable. In the first place, Neve tells us that more than three-fourths of all his epithelial cancers were of the peculiar "Kangri-burn" variety. During the cold winter, for the sake of warmth, the natives carry under their clothes, in contact with the lower part of the abdomen, a charcoal fire-basket ("Kangri"). This often causes burns of the skin of the abdomen, thigh, etc. As the result of constant irritation by the "Kangri," the resultant scars often become converted into thickened, raised excrescences, which eventually ulcerate. Foul, excavated, spreading ulcers, with thick raised edges, thus result. The adjacent lymph-glands become similarly affected, and often even the axillary glands as well. Death is commonly caused by septic complications, secondary to these sloughing ulcers, which sometimes perforate large bloodvessels, and prove fatal in this way. Excision of the disease in its early stage is absolutely curative; but after the glands have become extensively involved, only 50 per cent. of those operated on can be completely cured. The important question arises: What is the real nature of this malady, which is so different from ordinary epithelial cancer in its main features? According to Neve, it is cutaneous epithelial cancer, the hard fibrous base of the ulcers being infiltrated and overlaid by masses of epithelial new-formation, containing abundant "nests," etc. In all this, it seems to me, we scarcely have sufficient evidence of cancer, especially in view of the clinical course of the malady, its curability by operation, and the absence of metastases. The disease is probably more akin to keloid than to cancer; and, like the former, it is probably due to microbic infection.

If this peculiar affection is removed from the list of cancer, it will be seen that the latter malady is exceptionally rare in Kashmir.

Another noteworthy feature of Neve's statistics, compared with those of the Punjab, is the relative rarity of cancer of the penis. The uncircumcised of Kashmir have no special proclivity to this local variety of the disease, which supports my above-mentioned contention as to the non-cancerous nature of most of the Punjab penile cases.

The Kashmir data agree with those from the Punjab, in indicating great rarity of visceral cancer, specially of the stomach, liver etc.

With regard to sarcoma, of 154 cases, 23 were unclassified as to locality; of the others the sites were: gum (epulis), 21; neck, 12; parotid, 12; lower jaw, 9; upper jaw, 7; orbit,[1] 6; leg, 6; groin, 5; thigh, 5; forearm, 5; palate, 3; base of skull, 3; chest, 3; back, 3; elbow, 3; foot, 3 etc.

The most noteworthy feature of this list is the frequency of malignant "epulis." A few of the patients were young children.

Of 692 non-malignant tumours, the distribution was as follows: papilloma, 120; unclassified, 120; polypi, 114; lipoma, 106; fibroma, 57; granuloma, 38; horny, 29; nævus, 27; neuroma, 25; keloid, 18; chondroma, 9; osteoma, 6; lymphoma, 5; goitre, 4; myxoma, 2; molluscum fibrosum, 1 etc.

Of 213 cysts, the following subdivision is given: sebaceous, 124; ranula, 34; ovarian, 15; cystic goitre, 15; dermoid (mostly periorbital), 12; hydatid, 8; serous, 7; lactic, 2; mesenteric, 2; pancreatic, 1; parotid, 1 etc.

It is remarked of the sebaceous cysts, that they were singularly common in certain villages. A great many hydroceles (298) and ganglions (44) were also noted.

In *Assam*, according to Dr. Dalgetty,[2] malignant tumours are very rare. His experience relates to Adampore, in South Sylhet. During five years' work in this district, among a labouring population of 12,000 Hindoos—men, women, and children—imported from various parts of India to work in the tea-gardens, he met with only eight instances of malignant disease. These comprised six of cancer—viz., four males (one, aged thirty-five, of the tongue; one, aged forty-five, of lip; one, aged thirty-five, of mouth; one, aged thirty, of penis) and two females (both of the cervix uteri, at about the age of forty); and two of sarcoma (one, aged thirty-five, of the palmar fascia; one, aged thirty-five, of the rib).

Among these Hindoos, 2 cases of ovarian cystoma, 1 of uterine myoma, and 1 of lipoma of the breast, were also met with.

Of 15,000 resident natives, mostly Mohammedans, only three cases of malignant tumours were seen during the same period—viz., a male, aged fifty, with cancer of the lip; a male, aged thirty-five, with sarcoma of the scalp; a male, aged thirty, with melanotic sarcoma of the eye. One case of cystic myoma uteri was also seen.

Both sexes anoint the whole body with cocoanut oil; and are very free from warts and other cutaneous blemishes.

The district is highly malarious, and it may be safely asserted that every one of the above patients with malignant tumour had suffered from malaria.

Dr. Drake,[3] during several years' practice in the Thakurbarrie district of Assam, when he was in charge of several thousand coolies from various parts of India, as well as of the natives of the vicinity, testifies as to the rarity of malignant tumours; for he never saw a single case.

A valuable statistical study of the incidence of cancer among natives,

[1] In a recent publication Dr. Neve mentions the eye as also a fairly common seat of sarcoma in Kashmir. *British Medical Journal*, vol. i., 1906, p. 1217.

[2] *Journal of Tropical Medicine*, April 15, 1902, p. 122.

[3] *Lancet*, vol. ii., 1904, p. 1309.

in the surgical wards of the Medical College Hospital of Calcutta, during the nine years 1896-1904, has been published by Dr. Megaw.[1] In this series, the cases of cancer occurring in the medical and gynæcological wards of the hospital are not comprised. 11,446 surgical hospital patients furnished 343 cases of malignant tumours (1 in 33, or 3 per cent. of the total admissions). The natives of India are very loath to come to hospitals unless afflicted with very serious disease—hence "it is only natural that malignant tumours should bulk larger in Indian statistics than in those for Europe." The local conditions in the two cases are, in fact, so different that "no fair comparison as to the relative prevalence of the disease in India and Europe can be based on the above data." Although the carcinomatous form of the disease was more frequently met with than the sarcomatous, yet the ratio of the latter to the former was much higher than in Europe. The site-incidence percentage for carcinoma was as follows: penis and scrotum, 20; female breast, 19·9; integument, 15·2; antrum and palate, 9·9; rectum, 1·7; rodent ulcer, 1·7; tonsil, pharynx, and larynx, 1·7; stomach, 0·9 etc. For sarcoma the usual seats were: leg, 18·7; neck, 18·7; arm and axilla, 12·8; jaws and antrum, 10·1; wall of trunk, 7·2; testes, 5·4; face, 5·3; breast, 3·9; pharynx, 3·4; abdominal cavity, 3·4; pelvis, 2·9 etc.

The Hindoos were found to be more frequently affected with malignant disease than the Mohammedans, mainly owing to their greater proclivity to a few special local forms of the disease—viz., to "cancer" of the penis, sixty-four Hindoos being thus affected, and only two Mohammedans; to mammary cancer, fifty-seven Hindoo females being affected, as compared with only four Mohammedans, the latter having great reluctance to hospital treatment for their women. Hindoos were also more prone to cancer of the mouth, cheek, and jaws than the Mohammedans, in the proportion of 49 to 1, although both alike indulged in betel-chewing, to which this form of disease has often been ascribed.

Dr. McLeod,[2] from experience in *Calcutta* hospitals, concludes that malignant tumours are comparatively common among the natives of Bengal, both in hospital and private practice: in females the breast being chiefly affected, and in males the cutaneous system, oral cavity, and especially the penis. Of 254 tumours operated on at the Medical College Hospital in Calcutta (1879-1883), 49 were malignant; and of 333 tumours (1886-1890), 87 were malignant. Considering that the Bengal population, whence these hospital cases were derived, numbers over seventy millions, the proportion of cancer cases in these hospital statistics is surprisingly small.

According to Davidson,[3] cancer is very rare in Bombay, only 0·1 per 1,000 of the total deaths being due to this cause.

Dr. Niblock[4] has tabulated all the malignant tumours treated at the *Madras* General Hospital, during the ten years 1892-1901. To this

[1] *Indian Medical Gazette*, May, 1905, p. 163.
[2] "Operative Surgery in Calcutta," 1885, p. 102; also "International Text-Book of Surgery," vol. ii., 1900, p. 1206.
[3] "Geographical Pathology," 1892.
[4] *Indian Medical Gazette*, April, 1902, p. 161.

hospital patients come not only from the city of Madras, which has 500,000 inhabitants; but also from all parts of the Madras Presidency, which comprises a population of over 40,000,000, of whom three-quarters are Hindoos, and the rest chiefly Mohammedans. During the decade under consideration, 4,270 patients were treated for malignant tumours, or about 2·5 per cent. of the total admissions. From these figures it may be concluded that malignant disease is very rare in Madras.

Of 976 carcinomata (males 746, females 230), the localization was as follows: mouth, 411 (males 314, females 97); penis, 200 (all Hindoos); tongue, 64 (males 58, females 6); breast, 44 (all Hindoos except one Mohammedan female; males 5, females 38); uterus, 46 (all Hindoos); jaws, 34 (males 30, females 4); rectum, 33 (males 27, females 6); stomach, 21 (all Hindoos; males 14, females 7); liver, 18 (males 15, females 3); skin of lower limbs, 17 (males 11, females 6); rodent ulcer, 4 (males 3, females 1); and vagina, 3.

A noteworthy feature about the above data, is the very large proportion of cases of carcinoma of the mouth and tongue which they comprise, amounting to nearly half of the total. Niblock attributes this to the prevailing habit of "betel"-chewing. Among the inmates of the Lahore, Kashmir, and Assam hospitals, this local form of cancer was very little in evidence, and one wonders whether "betel"-chewing prevailed among them. Here, again, we meet with a very large proportion of cases of "cancer" of the penis, all among Hindoos, as at Lahore. The Hindoos of the great cities of India seem to have special proclivity for this local variety of the disease, but nothing of the kind is noticeable in the more rural districts of Assam and Kashmir.

Of 4,903 Hindoo patients, 97 had carcinoma, or 1·98 per cent.; while of 339 Mohammedan patients, 6 had carcinoma, or 1·76 per cent.

The Eurasians seemed to be less subject to cancer than any other native race; and, among the Hindoos, several of the patients were Brahmins.

Of 293 sarcomata (males 217, females 58, children 12), the sites of the disease were as follows: lower limbs, 70 cases (males 58, females 11, children 2); neck, 35 (males 24, females 9, children 2); jaws, 33 (males 24, females 9); upper limbs, 27 (males 25, females 2); trunk, 17 (males 12, females 3, children 2); face, 15 (males 9, females 3, children 3); scalp and skull, 13 (males 9, females 4).

Of the Hindoo hospital inmates, 0·67 per cent. had sarcoma; and of the Mohammedans, 0·49 per cent.

Among the natives of *Ceylon*, malignant tumours are very rare, the death-rate from this cause in 1897, being 5 per 100,000 inhabitants, or 1 in 563 of the total deaths. Of 63,030 patients treated at the chief hospitals[1] in 1900, 248 had some form of malignant tumour, or 1 in 254; and of 6,501 deaths of the hospital patients, 27 were due to malignant tumours, or 1 in 241. In the same year, 256 cases of non-malignant tumours were under hospital treatment.

According to Sir A. Perry,[2] the cancer mortality in 1903, was 1 in every 16,820 persons living, or about 6 per 100,000 inhabitants, the com-

[1] Colonial Report, No. 19, 1902. [2] Report on Cancer in British Colonies, 1905.

monest seats being the oral cavity and penis. The island is highly malarious. Tubercle is rare, the death-rate from this cause in 1903, being 91 per 100,000 living.

In *Burmah* and *Siam*, malignant tumours are perhaps rather more prevalent than in India. During four years' residence in Siam, Gowen[1] met with a few cases of carcinoma and sarcoma; but Rasch never saw a single case of sarcoma there. In Bangkok, according to Nightingale,[2] although malignant tumours are seldom seen by the doctors, they are probably less rare than is generally believed.

Among the *Laos* people, who occupy the region to the north of Siam, Hansen[3] found that malignant tumours were very rare. In three years' practice he only met with a single case.

In the hospitals and dispensaries of the federated *Malay States*,[4] during the year 1903, thirty-three deaths from malignant tumours were recorded, or one in fifty-eight of all the fatal cases treated. Altogether, during the year, 256 cases of malignant and 297 of non-malignant tumours were under treatment. Malarial affections are very prevalent; and there is a considerable tubercle incidence, especially of phthisis.

**General Survey of the Distribution of Cancer in Australasia and Oceania.**

Among the whites of Australia and New Zealand, cancer is much more prevalent than in any other part of Oceania, and also than in Asia; but its incidence is much less than in England, the cancer death-rate per 100,000 inhabitants for the whole of Australia being 57, or 1 in 20 of the total deaths (1900).

All the local authorities state that malignant growths are so exceeding rare as to be almost unknown, among the aborigines of both these countries. According to G. C. Adams,[5] the Australian aborigines are "practically immune" from cancer. In Victoria, of seventy deaths among aborigines registered during the years 1894-1900, only one was due to cancer. These natives are, however, very prone to tubercle, and especially to phthisis. The Australian aborigines are a disappearing race, who now form only an insignificant fraction of the total population, for they are estimated to number less than 20,000. During ten years' experience among the aborigines of Queensland, Dr. Roth[6] never saw a single malignant tumour. For a young country, the social evolution of Australia has of late pursued a peculiar course. Its immense territory is occupied by a mere handful of people—some 3,750,000—of whom the great bulk are clotted in a few large towns on the coast of the temperate region, where the style of living emulated is that of the capital cities of Europe. Under the influence of socialistic ideas, immigration is discouraged, although the declining birth-rate has already fallen to such an extent as to endanger the future of the race. Thus, the population is almost

[1] *Janus*, 1896, 1897, and 1899.
[2] *British Medical Journal*, vol. ii., 1902, p. 835.
[3] *Pacific Medical Journal*, January, 1902.
[4] Colonial Report for 1903.
[5] *Lancet*, vol. i., 1904, p. 424.
[6] Report on Cancer in British Colonies, 1905.

stagnant; and it contains an unduly large proportion of adult and elderly persons. Under this concatenation of artificial circumstances, and with the aid of the lavish expenditure of borrowed millions, a high standard of individual material comfort has been attained in this "worker's paradise." Owing to the cheapness of meat and the gluttonous habits of the people, the amount consumed per head is exceedingly high. Under these circumstances, the tubercle mortality has diminished, while the incidence of cancer has greatly increased.

A curious feature with regard to cancer is that males are now more prone to the disease than females, the respective death-rates for 1900, being 59 and 55; and this greater proclivity of males is found in all the different states of the Union.

In Australia, as in Europe, the cancer mortality of the capital-city districts is much higher than that of the rural districts, the rate for the former being 81·3 (or 6·4 per cent. of the total deaths from all causes), as against 44·7 for the latter (or 3·9 per cent. of the total mortality).

Another noteworthy fact about the Australian statistics is that, like those of the United States, they show malignant tumours to be much more prevalent among immigrants than among those born in the country.[1]

Thus, for all Australia, the cancer death-rate in 1900, was 57·3. Of this total, the British and foreign-born immigrants were responsible for 40·2, and the Australian-born for only 17·1. If only persons of thirty-five years of age and upwards are included, the figure for the total cancer death-rate will then be 195·3. Of this, the British and foreign-born account for 137·1, and the Australian-born for 58·2.[2] All the different races of immigrants in Australia, experience there a higher cancer mortality than prevails in their native countries. This applies, as previously mentioned, even to the Chinese. Hence it may be concluded that sudden and violent changes in the environment are, *per se*, potent factors in the causation of cancer.

The cancer death-rates for the various States in 1900, were as follows: Victoria, 72; South Australia, 59; New South Wales, 57; Tasmania, 56; Queensland, 46; West Australia, 30.

In *New Zealand*, where the conditions of existence and of social evolution somewhat resemble those of Australia, the leading morbid tendencies are also somewhat similar. Cancer and insanity have increased, and are increasing; while tubercle is declining. The people are prosperous, with a diminishing birth-rate; and immense quantities of flesh food—chiefly beef and mutton—are consumed. "Meat for breakfast, lunch, dinner, tea, supper, etc., just like the porridge-pot in Scotland," as Dr. G. Macdonald, of Dunedin, wrote in answer to my letter of inquiry. In New Zealand, as in Australia, cancer is more prevalent among males than among females. The cancer death-rate for the whole country in 1900, was 60.

Among the inhabitants of the *South Sea Islands*, cancer is most exceptional. Dr. Brennan,[3] in eleven years' experience, never saw a single case among natives of these islands labouring in Queensland.

[1] Immigrants now total only about 15 per cent. of the entire population.
[2] Adams, *op. cit.* [3] Report on Cancer in British Colonies, 1905.

In the *Fiji Islands,*[1] malignant tumours are very exceptional, since among the 120,000 non-European inhabitants, of whom the aborigines comprise nearly 98,000, the rest being Indian coolies, Melanesians, Polynesians, etc., only two deaths occurred from this cause during the year 1900; and there were also only two deaths from non-malignant tumours. In 1903, five Fijians (two being half-castes) died of malignant disease—viz., one of carcinoma (pylorus), and four of sarcoma (orbit, kidney, inferior maxilla, and face).

Sir W. MacGregor's experience[2] is to the same effect. He says: "I do not remember ever having operated on a Polynesian or Melanesian for cancer, though I have had to do so sometimes on Europeans in Fiji." These people are practically vegetarians, and phthisis was not known in Fiji until it was brought there by Europeans.

In *New Guinea*, malignant tumours are equally rare. "For nine and a half years," says MacGregor, "I never saw a case in British New Guinea; but at the end of that time there occurred an example of sarcoma of the tibia in a Papuan, who had for seven or eight years lived practically a European life, eating tinned Australian meat daily" etc. Malarial and venereal affections are very prevalent, and tuberculosis as well, lupus exedens also is common.

In *Borneo*, cancer is quite as rare as in New Guinea. Pagel,[3] who practised in North Bornea for ten years, never saw a single case; and Nieuwenhuis[4] had a similar experience.

In *Java* and *Sumatra* it is just the same, a single example of a malignant tumour in a native being esteemed a great rarity (Kohlbrügge, Van der Burg etc.).

In the *Philippine Islands* similar conditions prevail. Thus, of 631 deaths among natives at Manila,[5] during the month of February, 1903, in which the causation was known, there was not a single instance of cancer, but 78 deaths were due to phthisis.

### General Survey of the Distribution of Cancer in Africa.

No part of the world is believed to be so comparatively immune from cancerous diseases as Africa, and this applies to nearly all parts of the continent, but especially to its northern parts—Egypt, Tunis, Algeria etc.

A few years ago, desiring to ascertain the actual incidence of the disease in *Egypt*, I wrote to Dr. Engel, of Cairo, who is in charge of the Egyptian vital statistics, and he kindly supplied me with the following data:

Of 19,529 deaths among natives of Cairo during 1891, only 19 were due to cancer (females 10, males 9), or 1 in 1,028. In England, during the same year, the proportion of cancer deaths was 1 in 29.

Of 12,950 patients at the Kasr-el-Aini Hospital during the years

[1] Colonial Report, No. 19, 1902, p. 141.
[2] *Lancet,* vol. ii., 1900, p. 1057.
[3] *Deutsch. med. Woch.*, October 17, 1901.
[4] *Janus,* 1899.
[5] *Journal of Tropical Medicine,* July 1, 1904, p. 208.

1889-1891, only 77 were affected with cancer, or 0·6 per cent.; whereas, in London general hospitals at about the same period, I have ascertained that the proportion of cancer patients was 3·5 per cent.

From these data, it appears that the reputation of Egypt for comparative immunity from cancer is well founded.

In this Dr. F. C. Madden, of Cairo, concurs. Thus he says:[1] "The consensus of opinion among medical men in Egypt is, that cancer is never found either in male or female, among the black races of that country. These include the Berberines and the Sudanese, who are all Mussulmans, and live almost entirely upon vegetarian diet. Cancer is fairly common, however, among the Arabs and Copts, who live and eat somewhat after the manner of Europeans."

Griesinger states that he never met with a single case of cancer of the stomach, during many years' practice in Egypt.

Insanity is phenomenally rare in Egypt, but there is a fair amount of tuberculous disease, including phthisis; while malarial and venereal affections, including syphilis, are very common, "condylomata flourishing with tropical luxuriance" (Madden).

Several authors have called attention to the rarity of malignant tumours among the natives of *Algeria* (Legrain, Kirmisson etc.), and have ascribed this comparative immunity to their abstinence from animal food and intoxicating drinks.

The official statistics for Algeria[2] relate only to the towns, which comprise for the most part a large European element, as at Algiers, where the cancer death-rate in 1895, was 56 per 100,000 living; but at Oran, where there are but few Europeans, the cancer death-rate was only 1·3; while at Biskra, with nearly 8,000 inhabitants, at Batna, with over 6,000, at Mostaganem, with over 16,000 inhabitants, not a single death from cancer was registered; and at Guelma, with over 7,000 inhabitants, there was only one death from cancer.

Many travellers have commented on the rarity of cancer in *Tunisia;* and, according to Behold and Tiriant, it is not met with among the aborigines.

With regard to the incidence of cancerous diseases in *Morocco*, I am indebted to the late Ernest Hart for the following valuable information. In answer to my letter of inquiry, he very kindly wrote to Dr. Terry, of Tangiers, who replied as follows: "Cancers, sarcomas etc., do not seem to be very prevalent. At any rate, the number of cases met with, as compared with other diseases, show that they are of less frequent occurrence than in England. Among the inhabitants, who are of mixed Arab and native blood, I have seen cancers of the female breast, uterus, and of the tongue, as well as sarcomatous growths in various parts of the body."

In *Madeira* and the *Canary Islands* cancer is said to be oftener met with than in North Africa (Behla); but Dr. J. Goldschmidt[3] has found that the disease is decidedly rare in the former island.

[1] *British Medical Journal,* vol. ii., 1902, p. 730.
[2] *Statistique sanitaire des villes de France et d'Algèrie pendant l'annèe* 1895, p. 114.
[3] *Deutsche med. Woch.,* July 10, 1902.

Among the natives of the *Sudan* seen by Dr. A. Balfour [1] at Khartoum, instances of carcinoma and sarcoma were occasionally met with.

During his visit to *Somaliland* and *Erythrea* a few years ago, Fiaschi [2] was struck with the remarkable absence of malignant tumours among the crowds who flocked to his clinic, although tuberculous and syphilitic affections were common.

We have no recent information as to the incidence of these maladies in *Abyssinia*, but by the older writers they are said to be commoner in this country than in any other part of Africa. Dr. C. Singer,[3] who lately travelled through the south-west of Abyssinia, describes goitre and Graves' disease as being common; and in a Galla he saw a large osteoma of the ribs, but he makes no mention of having seen a single instance of cancer.

On the *West Coast* malignant tumours are very rare among the aborigines. Malaria is exceedingly prevalent, but tubercle is rare, except among natives who have acquired semi-civilized habits. The records of native patients treated at Bathurst, in Gambia, for many years contain not a single entry under cancer; and Dr. Forde,[4] during nine years' practice there, never saw a single case.

During the year 1903, of 9,068 patients (in 591, out 8,477) treated at Government hospitals etc., not a single instance of malignant or any other tumour was met with, throughout the Gambia colony.

In the Gold Coast colonies cancer is very rare, as it is also in Ashanti. During ten years' practice in the latter country, Dr. Henderson [5] never saw a single case.

According to Bornier,[6] cancer is never seen among the Senegal negroes. During fourteen years' practice at Lagos, Dr. O. Johnson [7] saw but five instances in natives, and these had all lived for many years a semi-civilized life, eating meat etc., like Europeans. Plehn met with only a few cases of sarcoma among the natives of the Cameroons. In British Nigeria, during 1900,[8] 5,690 natives were treated at the various hospitals and dispensaries, but not a single death from malignant tumour is recorded.

In *Uganda*, that Central African community where the indigenous civilization attained its maximum, malignant tumours, although very much less common than among Europeans, are said to be by no means rare. At Dr. Cook's hospital at Mengo,[9] cases of carcinoma of the lip, œsophagus, breast, uterus, intestine etc., have been under treatment; as well as cases of chondro-sarcoma of the parotid, sarcoma of the jaws, melanosis etc. Uterine myomata and ovarian cystomata are also fairly common, as well as various other non-malignant tumours, such as lipoma, fibroma, enchondroma, osteoma, nævus, sebaceous and dermoid cysts.

Although Uganda has a cool climate for Equatorial Africa, and lies

[1] *Journal of Tropical Medicine*, April 15, 1904, p. 118.
[2] *British Medical Journal*, 1897, vol. i., p. 687.
[3] *Journal of Tropical Medicine*, January 16, 1905, p. 17.
[4] Report on Cancer in British Colonies, 1905.
[5] *Ibid.*, 1905.
[6] *Path. Comparée*, etc., 1889, p. 254.
[7] *Lancet*, vol. ii., 1900, p. 1057.
[8] Colonial Report, No. 19, 1902, p. 190.
[9] *Journal of Tropical Medicine*, June 1, 1901, p. 173.

high, its mean elevation being 4,000 feet above the sea-level, malaria is exceedingly prevalent, constituting nearly 25 per cent. of all the cases treated. Syphilis also is rampant, 10·5 per cent. of the admissions being for this disease; while tuberculous maladies account only for 4 per cent. The country is hilly, and many of the people are affected with goitre and albinism. The natives are clean, intelligent, and "splendidly developed physically." Their staple food comprises plantains, bananas, and sweet potatoes, while banana wine is extensively consumed; but meat can seldom be obtained. In other parts of Central Africa cancer is decidedly very rare.[1] Thus, Dr. Scott, of the Zomba Mission, who has been in the country for fifteen years, has never seen a single case; and Dr. Morris, formerly of the Blantyre Mission, in four years' work saw only a single case. In like manner, Dr. Old, during four years' work there, met with only two cases of malignant disease, while Dr. Hearsey's[2] testimony is to the same effect.

Dr. A. R. Sieveking, now of Bristol, who practised for several years among the natives of *Masailand*, informs me that he never saw a single example of malignant tumour among them, although this part of the country was well stocked with big game, which formed an important part of the natives' food when they could get it.

Among the natives of the *Nyassaland* plateau, Dr. Kellett-Smith[3] found that all kinds of malignant tumours were so rare "as to be practically unknown." Although all scars tended to become keloid, yet these keloids never took on malignant properties. Syphilis seemed to be incapable of permanently establishing itself among the natives. Generally speaking, in British Central Africa malignant tumours are decidedly rare.

In *Mauritius* and the *Seychelles* cancer is also rare. At the former place, in 1903, 67 cases of cancer were met with among 21,356 hospital patients;[4] at the latter place, of 219 hospital patients, only 2 had cancer (both of the stomach). In the mixed population of *St. Helena* cancer is not uncommon.

Livingstone[5] speaks of cancer as being absent from the *Barotze* country, and among the Bakwains, although the latter are prone to fatty and fibrous tumours.

The natives of *Mashonaland* and *Bechuanaland* are said to be equally exempt.

In *Basutoland* malignant tumours are rare.[6] At the Leribe Hospital, 3,128 natives were treated in 1900, of whom 4 had malignant and 25 non-malignant tumours. Of 4,684 patients at the Maseru Dispensary in the same year, 2 had cancer and 44 various non-malignant tumours, including 6 cases of lipoma and 3 dermoid cysts. Of 2,679 natives treated at the Mafeking Hospital, 6 had cancer, 4 sarcoma, and 22 various non-malignant tumours; and at Quthing, of 1,242 patients, 2 had cancer and 7 non-malignant tumours (enchondroma, 3; fibroma, 2; lipoma, 2).

[1] Report on Cancer in British Colonies, 1905.
[2] *British Medical Journal*, 1906, vol. ii., p. 1562.
[3] *Liverpool Med.-Chir. Journal*, 1901, vol. xxi., p. 46.
[4] Report on Cancer in British Colonies, 1905.
[5] "Missionary Travels in South Africa," etc., pp. 127, 504.
[6] Colonial Report, No. 19, 1902, p. 25.

Cancer is very rare among the natives of *Natal*,[1] especially among those of Bantu origin, for out of a population of 86,000, with a general death-rate of 19 per 1,000, only one death was ascribed to this cause in 1903.

An example of a large sarcoma of the lumbo-sacral region in a Zulu, aged thirty, has lately been described by Dr. H. Goodman, of Johannesburg.[2]

According to Hawes,[3] cancer is very rare among the *Hottentots*. He has, however, met with three instances in natives of this race, one of whom had lived for many years as a servant in an English family.

Among the *Boers* and *Europeans* living in South Africa, who are large flesh-eaters, malignant tumours are common ; but among the natives, who are mainly vegetarians, these tumours are so rare as to be almost unknown.

### General Survey of the Distribution of Cancer in America.

Owing to the fact that compulsory death registration in the *United States* is confined to a limited area (comprising a population of about 29,000,000); while for the rest of the country (comprising a population of over 47,000,000), the statisticians have to depend for their information on the data supplied by the "enumerators," who—as we are told in the introduction of the official report[4]—often fail to make inquiry as to the cause of death, or, indeed, to make any return of deaths at all, the official reports compare unfavourably, so far as accuracy and reliability are concerned, with corresponding European publications.

In consequence of this unsatisfactory state of affairs, we have two estimates as to the incidence of cancer in the United States, the one based on the returns for the whole country, the other on the more reliable data for the "registration area."

According to the former, the cancer[5] death-rate in 1900, was 43 per 100,000 living, being 1 in 2,309 of the total population, or 1 in 31 of the total deaths.

According to the latter, the cancer death-rate[6] was 60 for the same year, being 1 in 1,665 of the total population, or 1 in 29 of the total deaths.

Of these two estimates, the latter is the more reliable ; but my impression is that both of them understate the incidence of the disease, which is, I expect, but little less in the United States than in Europe.

In the "registration area," the death-rates from the disease in the various states were as follows : Maine, 83 ; Vermont, 81 ; Columbia, 71 ; New Hampshire, 66 ; Massachusetts, 66 ; Rhode Island, 62 ; New York, 61 ; Connecticut, 61 ; Michigan, 58 ; and New Jersey, 50.

In the United States, as in Europe, Australia etc., the cancer mortality is increasing.

For the chief towns the rates were as follows : San Francisco, 112

[1] Report of Medical Officer of Health for Natal for the year 1903.
[2] *Transvaal Medical Journal*, May, 1906, p. 319.
[3] Bartholomew's Hospital Reports, vol. xli., 1906, p. 161.
[4] Twelfth Census Report of the United States, 1900, vol. iii., part i.
[5] Comprises cancer and tumour. [6] Without tumour.

(1900); Boston, 76 (1898); Philadelphia, 73 (1900); Baltimore, 69 (1904); New York, 64 (1900); New Orleans, 64 (1898); Chicago, 63 (1900); Buffalo, 53 (1899) etc.

The returns indicate greater prevalence of the disease in rural (death-rate 71), than in urban districts (death-rate 65); but, for the reasons above mentioned, too much importance should not be attached to these estimates.

Another source of fallacy in the United States vital statistics is that "cancer and tumour" are "considered together, as it is found impossible accurately to distinguish them, as they are commonly reported." [1]

In all parts of *British North America* cancer is fairly common among the whites, probably about as common as in the United States, but I have been unable to meet with any satisfactory recent statistics. Among the aborigines of Canada, Landry [2] (1861) found that cancer was exceedingly rare, and it is still very infrequent.

Of 3,275 necropsies at the chief Montreal hospitals (up to 1904), 275, or 1 in 11·9, were for cancer. This nearly corresponds with the ratio in German hospitals, which has been estimated at 1 in 12; and the Guy's Hospital records show, that 1 in 8 of all necropsies there are for cancer.

In the province of Ontario there were 1,055 deaths from malignant tumours, in 1900.

For some of the chief towns, the cancer death-rates per 100,000 living in 1891, were as follows: Halifax, 54; Quebec, 42; Montreal, 39; Toronto, 36; and St. John, 15. For Victoria (British Columbia) the rate was 110 in 1896.

In *Mexico* cancer is fairly common among those of European descent, who live in the high, cool regions, and even the semi-civilized natives and half-castes are affected; [3] but, according to Jourdanet, it is almost unknown in the low-lying hot regions.

In the *Central American* communities the disease is rare, the Guatemalan cancer death-rate for 1894, being only 4; and in British Honduras the malady is equally rare.

In the *Bermudas*,[4] malignant tumours are met with among those of white, as well as those of coloured descent; thus, of 423 deaths in 1900, 13 were due to this cause, or 1 in 33.

Of 145 deaths among whites, 8 (males 2, females 6) were due to cancer, or 1 in 18; of 278 deaths among the coloured, 5 (males 1, females 4) were due to this disease, or 1 in 56.

In the *Bahamas*,[5] with a population of 54,709 (mostly coloured), and a general mortality of 1,231, during the year 1900, there was only one death from cancer.

Generally speaking, cancer is decidedly rare in the *West Indies*, but more than half a century ago L. Young had noted occasional examples of it. Thus he says: [6] "Among West Indian negresses malignant disease of the uterus and mamma is of very rare occurrence, and even those

[1] Twelfth Census Report of United States, 1900, vol. iii., part i., p. clxxxi.
[2] *Bull. de la Soc. d'Anthropologie*, t. ii., p. 16.
[3] Rodman, "International Text-Book of Surgery," vol. ii., 1900, p. 731.
[4] Colonial Report, No. 19, 1902. [5] *Ibid.*, p. 20.
[6] Cited by Astley Cooper in his "Anatomy of the Breast," etc., 1840.

cases which I have witnessed in this class of people have been among the better orders of them, whose habits of living have been assimilated to those of Europeans."

In Jamaica the death-rate from this cause in 1888, was nearly 12 per 100,000 living, which in 1905 had increased to 19. The phthisis death-rate for the island amounted to 155 in 1903, and the average for 1895-1904 has been 160.

Of 1,317 deaths in the hospitals of Trinidad and Tobago[1] during 1900, 13 were due to malignant tumours, or about 1 in 102. The localities affected were the female genitalia in 5 cases, the liver in 3 cases, and 1 each of the mamma, stomach, and larynx. Fifty-five cases of non-malignant tumours were also treated at these hospitals, including 23 uterine myomata and 2 ovarian cysts.

In the various hospitals of Grenada,[2] in 1900, 490 patients were under treatment, of whom 8 had malignant tumours, or 1 in 62.

At St. Lucia,[3] of 2,810 hospital patients, with 159 deaths, in 1900, 5 were due to cancer, or 1 in 32 of the deaths. Twenty-two patients were treated for non-malignant tumours during the same year.

Of 30,856 natives of St. Kitts,[4] 899 died during 1900, malignant tumours being the cause of death in 4. Thus, the cancer death-rate per 100,000 living was nearly 13, or 1 in 225 of the total deaths.

Among the 2,463 Europeans, there was not a single death from this cause during the year.

At Nevis,[5] with a population of 14,520 natives, of whom 294 died during the year, there was not a single death from cancer.

In Anguilla,[6] with a native population of 4,424 and 55 deaths, only one death from cancer occurred during the year, the rectum being the part attacked. With regard to this case, the medical officer says in his report : " A few deaths from cancer are recorded as having occurred among the black population prior to my arrival in the island ; but, during my three years' residence here, I have only seen this one case of cancer among the blacks. The whites are, however, fairly often attacked, especially with ulcerated forms of cutaneous cancer." Thus, of 32 deaths among whites during the period 1892-1900, 5 were due to cancer ; whereas, of 479 deaths among the blacks during the same period, only 2 were due to this cause. Phthisis and malaria are common in the island.

In the tropical parts of *South America* cancer is decidedly rare among the natives.

In *British Guiana*,[7] of 148,221 patients treated at the public hospitals during the year 1903-1904, only 105 had malignant tumours ; and there were 93 instances of non-malignant tumours. Of 1,556 deaths in these hospitals during the same year, 27 were due to malignant disease. Malaria and tubercle are very prevalent, the latter malady causing 13·9 per cent. of all deaths.

Spitzly,[8] during a sojourn of eight years in the Surinam district of

[1] Colonial Report, No. 19, 1902. [2] *Ibid.*
[3] *Ibid.* [4] *Ibid.* [5] *Ibid.* [6] *Ibid.*
[7] Report of the Medical Department of British Guiana, 1903-1904.
[8] *British Medical Journal*, vol. i., 1902, p. 16.

*Dutch Guiana*, found that the various forms of malignant tumours were not very common there. He met with the following cases: cancer of the tongue in an escaped Cabyle convict, malignant disease of the glands of the neck in a Guiana-born Jew of fifty, melanotic sarcoma of the external auditory meatus in a coloured man from Niekerie, cancer of the tongue in a Chinaman, several cases of mammary cancer in Creole women, malignant disease of the bladder in a middle-aged coloured native of Paramaribo who was a prison warder, several cases of cancer of the lip and penis in coloured people who had always lived in Surinam, etc. Malaria is very prevalent in Dutch as in British Guiana.

Cancer is rare in *Brazil*, especially in the Equatorial regions, the death-rate from this cause for 1903, being only 4 per 100,000 living (Sodré).[1] The uterus is the part oftenest affected, gastro-intestinal localizations being comparatively rare. The maximum of frequency is attained in the province of Rio Grande do Sul. For Rio di Janeiro, with its population of 850,000, the cancer death-rate was about 26 per 100,000 living in 1904, the tubercle mortality being 287, that for malaria 70, and the general death-rate from all causes 2,050.

In *Uruguay* cancer is comparatively common, the death-rate from this cause in 1897, being 47, or 3·28 per cent. of the total deaths, and tubercle is prevalent.

In *Argentina* cancer is also fairly common, especially in Buenos Aires, where the rate in 1900, was 91. In the province of Tucuman, the cancer death-rate for 1898, was only 10.

[1] *Brazil Med.* (Rio di Janeiro), 1904, vol. xviii., p. 229.

# CHAPTER III

## THE INCREASE OF CANCER, AND ITS CONCOMITANTS

### Preliminary Review.

In the course of organic evolution some types of disease, like species, have diminished and become extinct, while others have increased and become more prevalent. In comparatively recent times typhus fever, leprosy, malaria, scurvy, plague, and dysentery have almost or quite disappeared from our country; small-pox and other zymotic diseases have greatly diminished; while phthisis and tuberculous affections are decidedly on the wane.

On the other hand, a small group of maladies, of which cancer is the chief, has steadily increased; and this in spite of progressive diminution in the general death-rate, with other signs of material prosperity. Of the other members of this group, insanity, suicide, alcoholism, diabetes, and diseases of the circulatory system, are the chief; while to these may be added premature births and congenital deformities.

In all modern communities, where the occidental type of civilization prevails—of which the chief characteristics are industrialism and urbanization, with great increase and widespread diffusion of material prosperity—a similar tendency is noticeable, especially as regards cancer, the incidence of this malady having doubled in frequency in periods of from twenty to thirty years, the annual increment of increase averaging from 3 to 5 per cent.

This tendency seems to be of comparatively recent origin. At any rate, cancer is a disease of great antiquity, which is known to have existed from the most remote times of which we have any record. The "Papyrus Ebers," which is believed to have been written about 1550 B.C., contains a short section on malignant and other tumours, from which it may be inferred that the cardinal features of these maladies were then well recognized. In the works of Hippocrates, who is believed to have flourished during the latter part of the fifth century B.C., malignant and other tumours are referred to; but, in the somewhat detailed enumeration of the various maladies prone to occur at the different periods of life, which is embodied in the "Aphorisms," no mention is made of cancer. From this omission, and from the comparative paucity of the references to cancer in the Hippocratic writings, I conclude this affection must then have been comparatively rare.

We have singularly little trustworthy information as to the prevalence of cancer in this country during the Middle Ages and at earlier periods; but from such indications as are available, it seems likely that the malady then was of much less frequent occurrence than in modern times. The exceptionally well-kept registers of Market Deeping (Lincolnshire), during the years 1711 to 1723, in a total of 387 deaths, show only two from cancer (one male and one female).[1]

A unique statistical study of cancer incidence, during the whole of the nineteenth century, has been made by Ekblom [2] for the small Swedish town of Fellingsbro. Taking the averages for the first and last decennial periods of the century, he found that the cancer death-rate had increased from 2·1 per 100,000 living in the former period, to 118 in the latter.

The data derived from the long experience of the Scottish Widows' Life Assurance Fund,[3] are also of value in this connexion. Thus, the proportion of deaths due to cancer, to the total mortality among the males assured since 1815, has shown the following increases:

| | Per Cent. |
|---|---|
| 1815 to 1844 .. .. .. .. | 0·93 |
| 1845 „ 1858 .. .. .. .. | 1·79 |
| 1859 „ 1866 .. .. .. .. | 3·00 |
| 1867 „ 1873 .. .. .. .. | 4·56 |
| 1874 „ 1880 .. .. .. .. | 4·93 |
| 1881 „ 1887 .. .. .. .. | 5·44 |
| 1888 „ 1894 .. .. .. .. | 6·88 |

The experience of the chief German Life Assurance Company, as lately reported by Juliusberger,[4] is to the same effect. Thus, the cancer mortality among males, in the period 1885-1889, amounted to 3·7 per cent. of the total deaths, and among females to 11·4 per cent.; whereas, for the period 1889-1895, the corresponding ratios were 11·4 for men and 12·9 for women.

## England and Wales.

### *Statistical Summary.*

In this country the civil registration of births, deaths, and marriages came into operation in 1837; and the first annual report of the Registrar-General (for the year ending June, 1838) was published in 1839, the cancer death-rate then being 166 per million living. In the sixty-eighth of these reports—for 1905—this rate had increased to 885, or more than fivefold.

In the very earliest years of registration, before the enumerating machinery had been perfected, the data elicited may have left something to be desired. We will therefore commence our study with the year 1840, when the national statistics, under the able direction of William Farr, had already acquired well-deserved reputation for reliability.

In that year 2,786 persons died of malignant disease in England and Wales, the proportion being 1 in 5,646 of the total population, 1 in 129 of the total mortality, or 177 per million living.

In 1905 the deaths due to this cause numbered 30,221, being 1 in 1,131 of the total population, 1 in 17 of the total mortality, or 885 per million living.

[1] *British Medical Journal*, vol. i., 1896, p. 915 (Newman).
[2] *Hygeia*, January, 1902.
[3] Causes of death among the assured in the Scottish Widows' Fund (C. Muirhead), 1902, Edin. Appendix.
[4] *Zeits. f. Krebsforschung*, 1905.

In this respect, the position occupied by cancer is unique, for no other malady can show such a great increase. Thus, whatever the etiological factors of cancer may be, it is evident that they are not constant in action; and, if capable of exacerbation in some circumstances, they may be amenable to diminution in others. In this direction, it seems to me, we may reasonably hope to discover indications that will show us how to check the increase of the malady, and even enable us eventually to greatly reduce its mortality.

I believe that the tendency to cancer may be increased by unsuitable modes of living, and *vice versâ*. We must therefore seek out those conditions which favour its development; and, by avoiding them, we shall then be able to effect our object. In my opinion, it is only by progress along such lines, that the prevention of cancer is ever likely to be effected.

In further illustration of this subject, I have compiled the following table (see p. 53), which shows the increments of increase during the long succession of years.

### *The Reality of the Increase.*

With these figures before us, and all that they imply, there can be no doubt as to the reality of the increase in the cancer mortality. Yet this has been called in question. The earliest objectors ascribed the registered augmentation to mere increase of population; but the futility of this is demonstrated by the fact that, while the population barely doubled (1850-1905), the cancer mortality increased more than sixfold.

Next the attempt was made to explain the increase as due to the average age of the population having advanced, and the consequent liability of greater numbers. To this the answer is that the saving of life in modern times has mainly been confined to the precancerous years of existence, the death-rates of males over thirty-five and of females over forty-five having remained almost stationary, while the numbers attaining old age have decreased. Hence only an infinitesimal fraction of the increased cancer mortality can be thus accounted for. Moreover, an increase in the cancer mortality is by no means a necessary corollary of the survival of augmented numbers to the cancer age, as the Irish mortality statistics show.

Another objection to the reality of the increase in cancer has been raised by Dr. A. Newsholme [1] and his followers. They maintain that the registered increase is only apparent, being due to improved diagnosis and more careful death certification. There is, however, far too much uniformity in the steadily progressive increments of increase, during the long succession of years, to furnish any warrant for such a suggestion; while, taken in its entirety, the increase is so enormous as to make this explanation seem quite far-fetched.

Moreover, if improved diagnosis and death certification have caused additions to the cancer total—which I do not deny—these same conditions have also caused subtractions from it. Thus, as the Registrar-General tells us in his fifty-fifth report, even up to the year 1880 such common diseases as "fibroid tumour," "polypus," and "lupus," were

[1] Proceedings of the Royal Society, 1893, vol. liv., p. 209.

TABLE SHOWING THE PREVALENCE OF CANCER AND ITS INCREASE IN ENGLAND AND WALES.

| Year. | Total Population. | Total Deaths. | Cancer Deaths. | Cancer Death-Rate per Million Living. | Proportion to Population. | Proportion to Total Deaths. |
|---|---|---|---|---|---|---|
| 1840 | 15,730,813 | 359,687 | 2786 | 177 | 1 to 5646 | 1 to 129 |
| 1850 | 17,773,324 | 368,995 | 4966 | 279 | 1 ,, 3579 | 1 ,, 74 |
| 1855 | 18,829,000 | 426,646 | 6016 | 319 | 1 ,, 3129 | 1 ,, 70 |
| 1860 | 19,902,713 | 422,721 | 6827 | 343 | 1 ,, 2915 | 1 ,, 62 |
| 1865 | 21,145,151 | 490,909 | 7922 | 372 | 1 ,, 2670 | 1 ,, 62 |
| 1870 | 22,501,316 | 515,329 | 9530 | 424 | 1 ,, 2361 | 1 ,, 54 |
| 1875 | 24,045,385 | 546,453 | 11,336 | 471 | 1 ,, 2121 | 1 ,, 48 |
| 1880 | 25,714,288 | 528,624 | 13,210 | 502 | 1 ,, 1946 | 1 ,, 40 |
| 1881 | 25,974,439 | 491,937 | 13,542 | 520 | 1 ,, 1918 | 1 ,, 36 |
| 1882 | 26,413,861 | 516,654 | 14,057 | 532 | 1 ,, 1879 | 1 ,, 36 |
| 1883 | 26,770,744 | 522,997 | 14,614 | 546 | 1 ,, 1763 | 1 ,, 35 |
| 1884 | 26,922,192 | 530,828 | 15,192 | 564 | 1 ,, 1772 | 1 ,, 35 |
| 1885 | 27,220,706 | 522,750 | 15,560 | 572 | 1 ,, 1749 | 1 ,, 33 |
| 1886 | 27,522,532 | 537,276 | 16,243 | 590 | 1 ,, 1694 | 1 ,, 33 |
| 1887 | 27,827,706 | 530,758 | 17,113 | 615 | 1 ,, 1626 | 1 ,, 31 |
| 1888 | 28,136,258 | 510,971 | 17,506 | 621 | 1 ,, 1607 | 1 ,, 29 |
| 1889 | 28,448,239 | 518,353 | 18,654 | 656 | 1 ,, 1525 | 1 ,, 30 |
| 1890 | 28,762,287 | 562,248 | 19,433 | 676 | 1 ,, 1480 | 1 ,, 28 |
| 1891 | 29,081,047 | 587,925 | 20,117 | 692 | 1 ,, 1445 | 1 ,, 29 |
| 1892 | 29,405,054 | 559,684 | 20,353 | 690 | 1 ,, 1445 | 1 ,, 27 |
| 1893 | 29,731,100 | 569,958 | 21,135 | 711 | 1 ,, 1407 | 1 ,, 27 |
| 1894 | 30,060,763 | 498,827 | 21,422 | 713 | 1 ,, 1403 | 1 ,, 23 |
| 1895 | 30,383,047 | 568,997 | 22,945 | 755 | 1 ,, 1324 | 1 ,, 24 |
| 1896 | 30,717,355 | 526,727 | 23,521 | 764 | 1 ,, 1306 | 1 ,, 22 |
| 1897 | 31,055,355 | 541,487 | 24,443 | 787 | 1 ,, 1270 | 1 ,, 22 |
| 1898 | 31,397,078 | 552,141 | 25,196 | 802 | 1 ,, 1246 | 1 ,, 22 |
| 1899 | 31,907,762 | 581,799 | 26,325 | 825 | 1 ,, 1212 | 1 ,, 22 |
| 1900 | 32,261,013 | 587,830 | 26,731 | 828 | 1 ,, 1207 | 1 ,, 22 |
| 1901 | 32,621,263 | 551,585 | 27,487 | 842 | 1 ,, 1186 | 1 ,, 20 |
| 1902 | 32,997,626 | 535,538 | 27,872 | 844 | 1 ,, 1183 | 1 ,, 19 |
| 1903 | 33,378,338 | 514,628 | 29,089 | 872 | 1 ,, 1174 | 1 ,, 17 |
| 1904 | 33,763,434 | 549,784 | 29,682 | 877 | 1 ,, 1138 | 1 ,, 18 |
| 1905 | 34,152,977 | 520,031 | 30,221 | 885 | 1 ,, 1131 | 1 ,, 17 |

usually classed as cancer. In like manner, many other morbid states, formerly often regarded as cancerous, are now relegated to other categories. It is hardly likely, then, that there is any validity in Newsholme's contention; which, as I will now proceed to show, is—in its main contention—a statistical sophism, based upon fallacious figures as well as upon fallacious reasoning.

It is claimed that there has been no increase in the registered cancer mortality, for those parts of the body in which the disease is readily "accessible," and therefore presumably easy of diagnosis, such as the uterus, the mamma, the tongue, the mouth, etc.; whereas, in "inaccessible" localities, such as the stomach, the liver, and the intestines, where diagnosis is presumed to be difficult, the increase is said to have been very marked.

With regard to this, I have to remark that, although cancer is a disease which often presents great diagnostic difficulties in the earlier stages of its course; yet, before the fatal termination is reached, such unmistakable signs as to the real nature of the malady usually appear, as preclude the very frequent occurrence then of erroneous diagnosis. The very large proportion of mistaken diagnoses in the cases tabulated by the Cancer Research Fund,[1] by Bollinger etc., simply show that these were specially selected lots of difficult hospital cases; and they cannot be regarded as being in any way typical of everyday experience. The diagnosis of *advanced* cancer is, indeed, generally not a very difficult matter, as compared with most diseases.

In support of this "no increase" hypothesis, reference has been made to some data derived from the Scottish Widows' Life Assurance Society, and to mortality statistics of Frankfort; but, as Dr. J. F. Payne [2] has pointed out, these seem to be a very inadequate basis on which to raise such a superstructure. Before accepting any such conclusion, we must inquire whether similar results are arrived at in larger populations, and under more representative conditions. In the Report of the Registrar-General for 1889, a table is given with the object of determining this very question, by analysing a certain representative selection of the deaths from cancer, during the years 1868 and 1888 respectively. The results thus obtained with regard to localization may be epitomized as follows:

| Males. | | | Females. | | |
|---|---|---|---|---|---|
| Per 100 Deaths from Malignant Disease. | | | Per 100 Deaths from Malignant Disease. | | |
| | 1868. | 1888. | | 1868. | 1888. |
| Stomach .. .. .. | 35·3 | 24·0 | Uterus .. .. .. | 38·0 | 31·4 |
| Liver .. .. .. | 12·0 | 14·9 | Mamma .. .. .. | 24·2 | 18·3 |
| Tongue and mouth .. | 8·0 | 7·2 | Stomach .. .. .. | 11·9 | 11·9 |
| Rectum .. .. .. | 7·8 | 8·9 | Liver and gall-bladder .. | 6·4 | 12·7 |
| Face .. .. .. | 6·3 | 3·2 | Rectum .. .. .. | 3·7 | 4·8 |
| Intestine (*ex* rectum) .. | 4·0 | 6·6 | Intestine (*ex* rectum) .. | 2·1 | 5·3 |
| All others .. .. | 26·6 | 35·2 | All others .. .. | 13·7 | 15·6 |
| | 100·0 | 100·0 | | 100·0 | 100·0 |

[1] *Sci. Rep.*, No. 2, part i., 1905, p. 18.

[2] *Lancet*, vol. ii., 1897, p. 765.

The net result of this inquiry is to show, that the increase of the disease has not been confined to one or to some few parts of the body, but that it has involved them all. It is specially noticeable that cancer of the stomach, the chief representative of the "inaccessible" group, shows less relative augmentation, especially in males, than any other local variety of the disease; and in both sexes, the death-rates from this form of cancer show less increase than those for cancer in general. Thus, in 1868, the death-rate for cancer of the stomach per 1,000,000 living, thirty-five years old and upwards, was, for males, 283·65, and for females 193·45; whereas in 1888, the figures were, for males, 346·15, and for females 277·75. Thus, the increase for males in the twenty years was 22 per cent., and for females 44 per cent.; but, during the same period, the death-rate for cancer in general increased 50 per cent.

If we compare modern statistics as to the site incidence of the disease, with older data collected by Marc d'Espine (Geneva, 1838-1855), and by Virchow (Würzbourg, 1852-1855), the localization ratios are seen to be very similar. Thus, d'Espine's statistics show 63·3 per cent. of digestive-system cancer (stomach, 45; liver etc., 12; intestines and rectum, 6·3); Virchow's 50·5 (stomach, 34·9; intestines, 8·1; liver etc., 7·5). With these the Registrar-General's data for 1900, may be contrasted, the total for the digestive system being 49 per cent. (stomach, 21·5; liver, 14·1; rectum, 7·1; intestines, 6·3). There is here no sign of any specially disproportionate increase of cancer of the digestive system; and it is the same with the other chief local seats of the disease—uterus 18·5 per cent. (Virchow), 15 (d'Espine), and 11·2 (Registrar-General, 1900) etc.

So far, therefore, as these analyses go, Newsholme's postulates are shown to be untenable. Since the year 1897, Dr. Tatham has introduced into the Registrar-General's Annual Reports, a table showing the localization of the disease for each year. Analysis of these tables, for the years 1897 and 1900 respectively, gives the following results:

| Males. | | | Females. | | |
|---|---|---|---|---|---|
| Per 100 Deaths from Malignant Disease. | | | Per 100 Deaths from Malignant Disease. | | |
| | 1897. | 1900. | | 1897. | 1900. |
| Stomach .. .. .. | 20·6 | 20·5 | Uterus .. .. .. | 23·5 | 22·5 |
| Liver .. .. .. | 14·2 | 13·9 | Breast .. .. .. | 15·5 | 15·8 |
| Rectum .. .. .. | 8·6 | 9·0 | Stomach .. .. .. | 11·3 | 13·8 |
| Tongue and mouth .. | 6·3 | 6·8 | Liver .. .. .. | 13·2 | 14·3 |
| Intestine (*ex* rectum) .. | 6·3 | 7·0 | Rectum .. .. .. | 5·2 | 5·2 |
| Œsophagus .. .. | 5·7 | 5·4 | Intestine (*ex* rectum) .. | 5·2 | 5·7 |
| Bladder .. .. .. | 3·3 | 2·8 | Ovary .. .. .. | 1·7 | 1·7 |
| Jaws .. .. .. | 3·0 | 2·3 | Œsophagus .. .. | 1·4 | 1·3 |
| Neck .. .. .. | 2·7 | 2·3 | Tongue and mouth .. | 1·3 | 0·6 |
| Pharynx, tonsils, etc. .. | 2·3 | 2·2 | Bladder .. .. .. | 0·8 | 0·9 |
| Larynx and trachea .. | 1·8 | 2·0 | Jaws .. .. .. | 0·6 | 0·6 |
| Testis and penis .. | 1·5 | 1·5 | Neck .. .. .. | 0·6 | 0·5 |
| | 76·3 | 75·7 | | 82·3 | 82·9 |
| All others .. .. | 23·7 | 24·3 | All others .. .. | 17·7 | 17·1 |
| | 100·0 | 100·0 | | 100·0 | 100·0 |

The general tenour of these results, accords with that shown in the preceding analysis. The proportionate localization ratios show that there has been no special increase in the "inaccessible" manifestations of the disease; and this is very noticeable in such organs as the stomach and liver, which comprise the great majority of this form of the disease. Here again, then, Newsholme's hypothesis is shown to be devoid of solid foundation.

Further confutation of this hypothesis comes from the work of Dr. Claud Muirhead, the medical officer of the Scottish Widows' Life Assurance Society,[1] who found that the cancer death-rate among the assured males, was nearly twice as great in 1881-1890, as it was in 1861-1870. In a society of this kind, whose members can command the services of highly skilled medical men, it is hardly likely that such a great increase could be due to improved diagnosis and death certification, especially as every death, where there was a suspicion of cancer, was carefully investigated. "I think it is evident," says Muirhead, "that the theory that this large increase was wholly or even largely caused by sudden increase of diagnostic skill among the class of medical men who certify causes of death to this society, is untenable." This contention is fully endorsed by an examination of the localization ratios in 512 fatal cases, in which the exact site of the disease was specified. From this it appears that the deaths from malignant disease of "inaccessible" parts (stomach, liver, etc.) *decreased* by 7·70 per cent. from 1874-1880 to 1888-1894; and the results thus obtained by comparing the percentages of actual deaths, were entirely in accord with those arrived at by comparing the respective death-rates. Thus the reality of the increase of the disease among the members of this society, was clearly demonstrated.

I find it quite impossible to believe that anything like the great increase in the cancer mortality, indicated by the foregoing table, can be accounted for by improved diagnosis, by more accurate death certification, by changes in classification, or by alterations in the age and sex distribution of the population etc.

In this connexion, some valuable evidence has lately been adduced by Dr. F. L. Hoffman, statistician to the Prudential Insurance Company of America.[2] He has found, for instance, that in Rhode Island, during the period from 1876-1880 to 1896-1900, cancer of the breast among women increased by 115 per cent.; and in the city of Philadelphia the same malady, during the period from 1861-1865 to 1896-1900, increased 179 per cent. Here there can be no question as to the disturbing influence of sex diversities, nor of "inaccessible" localization etc. Neither is there any known marked alteration in the age distribution of these women, that would account for this increase.

Another consideration of similar import is, that the increased cancer mortality has been diffused all over the country, instead of being limited to certain areas only; so that those localities which formerly had the highest, lowest, and average cancer death-rates, still preserve their dis-

[1] "The Causes of Death among the Assured in the Scottish Widows' Life Assurance Society," p. 13. Edinburgh, 1902.

[2] *Journal of the American Medical Association*, October 19, 1901, p. 101.

tinction in this respect, although the cancer mortality has everywhere augmented. Taking all these facts into consideration, there can, then, be no doubt as to the reality of the increase in the cancer mortality. When, therefore, Dr. Bashford says:[1] "There is nothing in the statistical investigations of the Imperial Cancer Research Fund, which points to an actual increase in the death-rate from cancer:" I reply, that investigations conceived and executed in such an exceedingly faulty and imperfect manner, as those referred to, could not be expected to yield results having any scientific validity.

### *The Disproportionate Increase among Men.*

The Registrar-General's Annual Reports show that more women die from malignant disease than men, and this has been the case ever since these reports were first issued (1839).[2] In the year 1900, this disease was fatal to 16,246 females and to 10,475 males. For females the death-rate was 975 per 1,000,000 living of that sex, for males 672. In other words, 1 in 15 of all men, and 1 in 9 of all women, thirty-five years old and upwards, eventually died of cancer. The cancer mortality among males in that year, exceeded the decennial average for the male sex by 16 per cent.; and among females by 10 per cent. Attention is thus drawn to the remarkable fact, that the increasing cancer mortality is affecting, and for many years has affected, males to a much greater extent than females. The difference between the sexes in respect to their proclivity to malignant disease, has thus been steadily diminishing ever since 1850, as is shown by the following table:

TABLE SHOWING THE INCREASE OF MALIGNANT DISEASE AMONG MALES AND FEMALES PER MILLION LIVING.

| Period. | Male Cancer Death-rate. | Female Cancer Death-rate. | Sex Ratio. |
|---|---|---|---|
| 1851 to 1860 .. | 195 | 434 | 1 to 2·2 |
| 1861 „ 1870 .. | 244 | 523 | 1 „ 2·1 |
| 1871 „ 1880 .. | 315 | 622 | 1 „ 1·9 |
| 1881 „ 1890 .. | 430 | 739 | 1 „ 1·7 |
| 1891 „ 1900 .. | 597 | 903 | 1 „ 1·5 |
| 1901 „ 1905 .. | 723 | 997 | 1 „ 1·3 |

It thus appears that, although there has been a great increase of malignant disease in both sexes during the last half-century, and although at the present time more women are affected than men, yet the malady has augmented much more rapidly among the latter than among the former. Moreover, it is noticeable that the average age of English women is higher than that of men, so that the death-rates, as given above, are unduly favourable to the female sex.

It seems likely, if this disproportionate increase of cancer among males is not checked, that the disease will soon be as prevalent among

[1] *Sci. Rep.*, No. 2, part i., 1905.

[2] In 1838, 620 males and 1,828 females died of cancer, the respective death-rates being 84 for males and 240 for females, or 1 male to 2·74 females.

men as among women; or the comparative proclivity of the sexes in the respect may be reversed,[1] as has already happened in a few countries—*e.g.*, Australia, New Zealand etc.

The greater prevalence of malignant disease among women, is entirely due to the frequency with which, in them, the mammæ and uterus are affected, the corresponding structures in males very rarely originating the disease; while, in all other localities, the male liability is the greater.

Here it may be noted that the comparative proclivity of women to non-malignant tumours and cysts, is even more considerable than it is to cancer; and this also arises from the fact that, in them, the reproductive organs, especially the uterus and ovaries, very frequently originate tumours of this kind, whereas the corresponding male organs are seldom affected.

Another point worthy of notice in this connexion is that, for both sexes, the percentage of cancer deaths at ages above forty-five is greater than it used to be, the disproportionate increase in the male cancer mortality being mainly due to excessive incidence of the disease at comparatively advanced ages.

If now we ask, What is the cause of this disproportionate increase of cancer among men? Newsholme, De Bovis, and others reply: There has been no real increase, but the apparent augmentation is due to improved diagnosis and death certification, owing to the majority of cancers in men being of the "inaccessible" variety, which is difficult to discriminate. As I have, in the foregoing remarks, fully exposed the fallaciousness of this hypothesis, I need not further revert to the matter here.

It seems to me probable that this undue incidence of the increasing cancer mortality in men, may be ascribed to the fact that of late, as the result of urbanization, the conditions of life for men have come to resemble more closely those for women than heretofore. It is undeniable that urbanization has affected far more profoundly the natural life of men—altering, modifying, and suppressing their ancestral habits—than it has the natural life of women. Out of these conditions, which comprise a more domesticated mode of life, want of proper exercise, and excess of food, I believe the present increased cancer mortality has sprung.

### *The Concomitant Decline of Tubercle.*

Cancer is a disease more to be dreaded than tubercle, under the conditions of existence at present obtaining in modern communities where the occidental type of civilization prevails; for, while tubercle has declined

[1] During the twenty years comprised between the decennia 1851-1860 and 1871-1880, the increase for males was at the rate of 2·4 per cent. per annum, and for females 1·8 per cent. During the period between 1861-1870 and 1891-1897 the annual average increase for males was 3·1 per cent., and for females 1·9 per cent. "Should equal percentages of increase be maintained, they would bring up the cancer mortality rate to 1871 per million, for both males and females about the year 1932; and thereafter the rate for males would exceed that for females" (Tatham). The same disparity is shown if we restrict our field to persons aged thirty-five and upwards; thus, in 1885, 1 in 21 men, and 1 in 12 women of this age limit, eventually died of cancer; whereas, in 1905, the corresponding figures were 1 in 12 men, and 1 in 8 women.

with great rapidity, cancer has increased at a still faster rate, and these inversely related changes are still in active progress. In illustration of these remarks, it may be mentioned that during the last half of the nineteenth century, the cancer mortality for our country tripled; while, during the same period, the tubercle death-rate declined to the extent of nearly one-half. If we extend our survey, so as to embrace the sixty-five years from 1838 to 1903, these peculiarities are rendered still more evident; for, during this period, the increase in the cancer mortality was more than fivefold—viz., from 16 per 100,000 living in 1838, to 87 in 1903; whereas the phthisis mortality, in the same time, decreased more than threefold—viz., from 380 in 1838, to 119 in 1903. Moreover, the latest ascertained cancer death-rate (88 for 1905) is the highest on record; while that for phthisis (114 in 1905) is the lowest.

Cancer is now a more fatal disease for women than phthisis, the respective death-rates for 1905, being 100 for the former and 94 for the latter malady;[1] it was in 1903 that cancer first gained this lead.

Unless some great change in the national habits soon takes place, of which there is at present no well-marked indication, cancer will ere long claim more victims even than phthisis, as is already the case in many localities—*e.g.*, Hampstead, Clifton, Bath etc.

This great decline in the tubercle mortality under modern conditions of existence, is one of the most remarkable and unexpected facts that the study of vital statistics has revealed; and, rightly apprehended, it throws a striking light on the problem of the increase of cancer.

This correlated variability in morbid proclivity is met with in every community, where the modern type of civilization prevails; for in those parts where apparent exceptions occur, as in some districts of Ireland, this type of civilization, with its material prosperity, good food, and good sanitation, is conspicuous by its absence, as I have ascertained by personal investigation on the spot, with regard to Kerry and the "Wild West" of Ireland.

In point of time, these two movements have been coeval, as is shown by the following table, indicating the respective death-rates per million living, during the latter half of the nineteenth century:

| | 1851-1860. | 1861-1870. | 1871-1880. | 1881-1890. | 1891-1900. |
|---|---|---|---|---|---|
| Cancer .. .. .. | 317 | 384 | 468 | 589 | 754 |
| Phthisis .. .. .. | 2676 | 2475 | 2116 | 1724 | 1391 |
| Other tuberculous diseases | 807 | 765 | 747 | 696 | 619 |

This table shows that, for the country as a whole, the incidence of cancer and tubercle vary inversely.

It is a curious fact, that in many other of the inter-relations of these two diseases, an inverse relationship is also noticeable, as I shall have occasion to indicate in the sequel.

In this country a comparatively high and increasing cancer mortality

[1] The cancer death-rates, for 1905, are 75·6 for males and 100·5 for females; the corresponding phthisis rates being, for males, 134·7 and, for females, 94·7.

implies, according to its extent, a comparatively low and decreasing tubercle mortality, and *vice versâ*.

A similar connexity is noticeable, even where we confine our attention only to certain limited areas, as Haviland [1] has very clearly demonstrated. He worked out the death-rates for each of these diseases, for every one of the 630 registration districts, with such corrections for age and sex distribution as the available data permitted. He proceeded to indicate on each of two identical maps, the varying death-rates from each malady, by colouring the different areas—blue for those above the average, and red for those below, with intermediate tints for the corresponding degrees of mortality. Having completed this laborious task, he found, on comparing the two maps, that just such inter-relations as those above mentioned, prevailed in almost every district.

Some years ago, William Farr [2] selected thirteen registration districts, widely separated from one another, as examples of the favourable influence of improved sanitation, good drainage, and good water-supply on the public health. During the three decennia over which this inquiry extended, all the selected districts showed progressive declines in the general death-rate, as well as in the tubercle mortality; yet, in spite of these gains, the cancer death-rates were shown to have markedly increased, in every one of these thirteen districts.

Within the limits of individual large towns, as I shall presently have occasion to prove, a similar state of affairs is almost everywhere noticeable. Where the population is densest, there the tubercle mortality is highest; and it is just in these densely populated areas that the cancer mortality is lowest.

The increase of cancer and the decrease of phthisis in London during the latter half of the nineteenth century, are shown by the following data: [3]

| | Cancer Death-rate per 100,000 Living. | Phthisis Death-rate. |
|---|---|---|
| 1851 to 1860 | 42 | 286 |
| 1861 „ 1870 | 48 | 284 |
| 1871 „ 1880 | 55 | 251 |
| 1881 „ 1890 | 68 | 209 |
| 1891 „ 1900 | 84 | 183 |

For subsequent years the figures are:

| | | |
|---|---|---|
| 1901 | 88 | 171 |
| 1902 | 93 | 160 |
| 1903 | 96 | 155 |
| 1904 | 92 | 162 |
| 1905 | 93 | 142 |

The Report of the Medical Officer of Health for 1903, shows that well-to-do, salubrious Hampstead has the highest cancer death-rate of any Metropolitan borough—viz., 120 per 100,000 living [4]—while its death-

[1] "Geographical Distribution of Disease in Great Britain," 2nd edit., 1892; also his earlier work, "Geography of Heart Disease, Cancer, and Phthisis," 1875.
[2] Registrar-General's Thirty-seventh Annual Report.
[3] Report of the Medical Officer of Health of the County of London for 1903.
[4] Corrected for age and sex distribution, for hospitals, etc.

rate from phthisis is the lowest—viz., 73. Next to Hampstead, the wealthy communities of Marylebone (comprising some of the best residential quarters of the West End), and Chelsea suffer most from cancer, their respective death-rates from this cause being 119 and 106; while their mortality from phthisis is decidedly below the average (155)—viz., 151 and 149 respectively.

Of the six metropolitan boroughs having the highest phthisis mortality—viz., Holborn, Shoreditch, Southwark, Finsbury, Bethnal Green, and Stepney—only one, Southwark, has a cancer death-rate above the average (96), its figure being 104, and this is an exceptional occurrence.

Wandsworth, with a cancer death-rate of 102, has the low phthisis death-rate of 96.

As another example of this connexity, the case of Bristol may be instanced, with its well-to-do and salubrious suburb Clifton, and its busy working-class and comparatively poor district of St. Philip, for which the respective mortality data in 1903, were as follows:

| | Bristol. | Clifton. | St. Philip. |
|---|---|---|---|
| Total population | 338,895 | 44,435 | 48,986 |
| Total deaths | 4822 | 494 | 711 |
| General death-rate | 142 | 111 | 145 |
| Cancer deaths | 281 | 46 | 38 |
| Cancer death-rate | 83 | 103 | 77 |
| Phthisis deaths | 366 | 29 | 55 |
| Phthisis death-rate | 103 | 65 | 110 |

In nearly all modern communities where statistical data are published, similar relations prevail between these two diseases, of which I shall subsequently have occasion to cite many instances. Thus, Hungary, with the lowest cancer death-rate of any country in Europe (33), has the highest tubercle mortality (387). International vital statistics are, however, at present in too backward a condition to enable us to make a really satisfactory study of these inter-relations in every community. Thus, for France, Denmark, and Sweden, the available data refer only to the town population, which in these communities comprises only a small part of the total population; then, as to Switzerland, there are no official data for the whole country. Moreover, several communities are now in such a state of acute transition, owing to the sudden swarming to the towns etc., as to render their vital statistics for the time being unreliable for such comparisons.

In this connexion it is worth noting that the increase of cancer and the decline of tubercle, seem to have set in earlier in Great Britain than in other countries. Moreover, the British vital statistics are unusually complete and accurate with regard to these matters; and they have the further great advantage of having been compiled on a uniform plan, for a long series of years.

I regard this decline in the prevalence of tuberculous disease, as the direct outcome of the better food and improved hygienic conditions, for which we are indebted to our increased national prosperity; and I shall endeavour to show that conditions of this kind, by their action in another direction, are also mainly responsible for the augmented cancer mortality.

Moreover, it seems to me exceedingly probable, from considerations derived mainly from the study of the family history of cancer patients, that many of those thus saved from tubercle, eventually perish from cancer. Indeed, I think the increase in the latter disease has largely been brought about in this way.

Indigence, insufficiency of food, overcrowding, and bad sanitation, which favour the generation of most diseases, especially tuberculous and contagious affections, exercise no such power over the incidence of cancer, which flourishes most under just the opposite conditions.

### *Etiological.*

The precise period at which these remarkable changes in the morbid proclivities of the population commenced, probably dates back to the latter part of the eighteenth century; at any rate, they were certainly in operation during the whole of the nineteenth century.

It is in the spread of industrialism that their origin will be found, and especially in that particular phase of it, characterized by the utilization of steam as a motive power.

This kind of progress has entailed two remarkable effects: (1) *urbanization*, the most stupendous environmental change that the human race has ever experienced; and (2) enormous increase of riches with widespread material *prosperity*.

It now remains for me to show how, by the interaction of these factors, cancer has increased, while tubercle and other maladies have markedly diminished.

1. It is generally agreed that the stability of the equilibration of the constituent elements of living bodies, is more profoundly affected by sudden and violent changes in the environment, than by any other group of circumstances. The invariable tendency of such changes is to render the organisms that survive them more plastic—that is to say, more prone to deviate from the normal routine of their growth and development. The natural history of cancer shows that it is a disease belonging to this category. Any sudden, far-reaching, environmental change of some duration is probably potent in this direction, as may be inferred from the undue proclivity to cancer of immigrants into the United States, Australia, New Zealand, etc., to which I have previously called attention; and there are good reasons for believing, as I shall subsequently have occasion to indicate, that the sudden change from poverty and want, to riches and plenty may, *per se*, be equally potent—*e.g.*, Switzerland, Denmark etc.

The nineteenth century has been variously called the age of steam, the age of iron, the age of factories and industrialism, the age of natural science, the age of the microscope and of the microbe, according to the standpoint of the individual observers; but, for the great majority of the Western world, the past century will for ever be memorable as the age of urbanization. This tremendous vicissitude, suddenly precipitated, undoubtedly constitutes the most profound and far-reaching environmental change, that the human race has ever experienced ; and in England, where 80 per cent. of the population are now town-dwellers, it has gone further than in any other community. The last century has witnessed the transition of millions of people from rural life and surroundings, to life in large towns, where all the conditions of existence are so different. I believe that the increase of cancer in this country, has sprung out of impulses thus determined.

Until the advent of the nineteenth century an open-air existence had, from time immemorial, been the lot of the great majority of English people, who depended for subsistence mainly upon agricultural pursuits. Since that time this old-established mode of life has been radically and rapidly changed.

The first official enumeration of the population was made in 1801, when, of the 9,000,000 of people, more than three-fourths lived in the country. A century later, in 1901, the population had increased to over 32,500,000, of whom less than one-fourth now lived in the country.

In 1801, there were in England and Wales sixty-one towns, with a population of 2,163,698 inhabitants ; in 1851, these towns had increased to 580, and their population to 6,254,251, or 35 per cent. of the entire population. Twenty years later, in 1871, the towns numbered 938, and their population was 14,000,000, or 61 per cent. of the entire population ; in 1881, over 70 per cent. of the population was urban ; in 1891 this proportion had increased to nearly 72 per cent. ; and, in 1901, the town dwellers comprised 77 per cent. of the entire population. The urbanization of the English people is now wellnigh complete, for most of the present so-called rural population are suburbanites, or immigrants from the towns. Moreover, the towns have now become the chief breeding-grounds for the replenishment of the race, the rural population having lost its former productiveness in this respect.

Thus, in the course of a comparatively brief span, the conditions of existence for the whole nation have undergone more profound changes, than hundreds of centuries had previously wrought.

2. One of the most potent and widespread effects of the conditions of life incidental to urbanization, on the health of those involved in its influence, is its tendency to induce degenerative changes which impair the capacity of those affected to resist various morbid excitations. It will probably be found that these changes ultimately depend upon perverted cellular metabolism, which is, I believe, the common root whence spring such diverse morbid manifestations as tubercle, cancer, and insanity.

Tubercle is a malady naturally tending to increase with increasing density of population, and especially with urbanization. If, therefore, this malady has not only been arrested, but has immensely declined, in spite of the rapid spread of urbanization, there must be some good reason for it.

This reason is sufficiently obvious. It is the unexampled increase in material prosperity, which the new conditions of existence have brought with them. Prosperity has given our people good food and good sanitation; and thus the evil tendencies of urbanization have, to a certain extent, been mitigated. Many of those who have acquired morbid predispositions owing to urbanization, now escape the fate that would have overtaken them under other conditions. It would, however, be a mistake on this account to regard such persons as being normally constituted. Their degeneracy is none the less real because it is not obviously manifest. According to my belief, it is from such persons and their descendants, that the ranks of the great cancer army are being constantly recruited. This view of the question throws an interesting sidelight on the curious paradox, in which there certainly is much truth, that a high cancer mortality is an indication of general prosperity and good sanitary conditions.

Probably no single factor is more potent in determining the outbreak of cancer in the predisposed, than excessive feeding. There can be no doubt that the greed for food manifested by the people of modern communities, is altogether out of proportion to the requirements of their present mode of life. Many indications point to the gluttonous consumption of proteids—especially meat—which is such a characteristic feature of the age, as likely to be specially harmful in this respect. Statistics show that the consumption of meat has for many years been increasing by leaps and bounds;[1] and it has now reached the amazing total of 130 pounds per head per year (men, women, and children), which is nearly double what it was half a century ago, when the conditions of life were less incompatible with high feeding. Among the well-to-do classes, the meat consumption has been estimated to amount to from 180 to 330 pounds per head per year. In addition to these totals, large quantities of game, poultry, rabbits, etc., must be included, as well as a fish consumption of 75 pounds per head per year, 12 pounds of cheese, 14 gallons of milk, and 80 eggs each a year.

When excessive quantities of such highly stimulating forms of nutriment are ingested by persons whose cellular metabolism is perverted, it seems probable that there may thus be excited, in those parts of the body where vital processes are still capable of rejuvenescence, such excessive and disorderly cellular proliferation as may eventuate in cancer. No doubt other factors co-operate besides those I have already mentioned, and among these I should be inclined to name deficient exercise, and probably also lack of sufficient fresh vegetable food.

Such influences as are comprised under the terms alimentation and domestication, seem to me to be of paramount importance in the ætiology of cancer.

With regard to the influence of diet rich in proteids on the incidence of tubercle, I think there can be no doubt that its effect is just the converse of that which we have seen in the case of cancer. That is to say, when the proportion of proteids, especially meat, in the dietary is too small, tubercle is very apt to supervene, even when climatic and hygienic conditions are favourable; and, besides the proteids of meat, the fats also seem to have anti-tuberculous properties.

[1] Report of Committee of Royal Statistical Society of Great Britain, December, 1904; for other data see also Mulhall's great work, "The Industries and Wealth of Nations," 1896.

As an example of this, the case of Ireland may be cited, where, as indicated in the preceding chapter, conditions of existence which are predominantly rural, are associated with poverty and a diet unduly deficient in proteids.[1] Under these circumstances, the cancer mortality is much lower than in England, while that from tubercle and phthisis is much higher; and this in spite of the more favourable climatic conditions and rural surroundings. Moreover, it is significant that in the "Wild West"—*e.g.*, in Kerry, where these conditions are most *en évidence*, and the people are notoriously underfed—the cancer mortality is the lowest in the United Kingdom, while the tubercle mortality is exceedingly high.

*Per contra*, in the one part of Ireland where industrialism and its concomitants have made marked progress, and where material prosperity is most noticeable—*e.g.*, in Ulster—the cancer death-rate is the highest, while that from phthisis is comparatively low.

In fact, the increased cancer mortality in Ireland during recent years, is mainly due to the augmentation of the malady among the industrial population of Ulster, Dublin etc.

It now remains for me to indicate briefly some of the salient features as to the extraordinary prosperity, with which this increase of cancer has coincided. It is all the more necessary for me to do this, because some pathologists still entertain and teach very erroneous views on this subject. These have received their apotheosis from Sir W. J. Sinclair,[2] who says: "If we could place all the lower orders who suffer from privation and depressing environment, for a generation or two in the position of the more favoured, we should stamp out cancer."

As all the information at my disposal is totally opposed to any such conclusion, it seems desirable to briefly review this evidence.

During the last half-century the wealth of the community has more than doubled, and is now estimated to amount to 15,000 millions sterling, the annual income being 1,750 millions. The present annual expenditure is estimated at 1,386 millions, of which 468 millions, or 34 per cent., is spent on food and drink (Giffen); and in the case of the working classes, 50 per cent. of their earnings are thus spent. During this period the income-tax assessments have increased from 300 millions to 833 millions sterling. This country is still the wealthiest in the world, although its wealth is proportionally less widely diffused among the people than is the case in many other countries. That the great mass of our people have, however, largely participated is evidenced by the fact that the accumulated savings of the working classes now total 531 millions sterling; and by such other considerations as I will now proceed to mention.

Pauperism has diminished by more than one-half—viz., from 5·3 per cent. of the total population in 1851 to 2·4 in 1901—and it is now less than at any previous period of our history. Crime, likewise, has steadily declined.

Wages have gone up as much as from 25 to 50 per cent.; while, at

[1] In 1895 the meat consumption of Ireland was estimated by Mulhall at only 40 pounds per head per year, or barely a third of the amount consumed in England.

[2] Allbutt's "System of Gynæcology," 1897, p. 657.

the same time, the prices of all the really essential commodities of life have fallen to an extraordinary extent.[1]

In the same time the consumption of meat per head has more than doubled.

The general death-rate declined from 22·7 in 1851-1855, to 18·2 in 1900, to 15·2 in 1903 ; and the population has steadily increased.

The mortality from zymotic, tuberculous, and many other diseases, has markedly diminished, and sanitary conditions have greatly improved. In short, the bulk of the people are better paid, better housed, and better fed than ever they have been before—that is to say, just such conditions have prevailed as Sinclair alleges are necessary to stamp out cancer—yet, instead of having decreased during this period, the cancer mortality has tripled.

In further support of my contention, I would point out that the Registrar-General's Reports show that the cancer mortality is *lowest* where the conditions of life are hardest, the surroundings the most squalid, the density of population greatest, the tubercle mortality highest, the general and infantile mortality highest, and where sanitation is least perfect—in short, among the poor of the industrial classes in our great towns ; whereas, among the wealthy and well-to-do, where the standard of health is at its best, and life is easiest, and where all the conditions of existence are just the converse of the foregoing, there the cancer mortality is highest, as I shall subsequently have occasion to show more in detail.

As an indication in the same direction, the experience of those engaged in prisons, workhouses, and lunatic asylums may be cited ; which is to the effect that cancer is comparatively rare among the inmates of such institutions, as it is also among the intemperate. Of like import is the fact that cancer is so fearfully common in civilized communities ; whereas, among savages, it is almost unknown. Moreover, in the animal world, it is among the domesticated varieties that malignant and other tumours are usually met with : in a state of nature such diseases are almost unknown.

That cancer is a disease of persons whose previous life has been healthy, and whose nutritive vigour seems to promise long life, is a statement in which I entirely concur. Long-continued observation of cancer patients, in the early stage of the disease, has convinced me that most of those affected are large, well-nourished persons, who appear to be overflowing with vitality. Such types are indicative of hypernutrition. The small, pale, ill-nourished, and overworked women, of the type so familiar in Lancashire and other industrial centres, are seldom afflicted with this disease.

The natural functions of female cancer patients are performed with ease and regularity. Their sexual health is vigorous, the capacity for reproduction beginning earlier and lasting longer than in the generality

[1] The Report of the Royal Commission on Agriculture (1897) shows: "That during the last quarter of a century there has been a fall of over 40 per cent. in the price of staple cereals, which in the case of wheat is 50 per cent. ; that in beef the fall has been from 24 to 40 per cent., and in mutton from 20 to 30 per cent. ; in dairy produce the price declined 30 per cent. ; in potatoes 20 to 30 per cent.," etc.

of women. Just so is it with regard to marriage, for a greater proportion of these cancer patients marry than of the female population in general. Moreover, they marry earlier, and commence to have children sooner, than the generality of married women ; and their fertility is much above the average. All these things indicate a certain vital exuberance, which is characteristic.

The great majority of such persons whose life-history I have investigated, have been well fed and well housed, having had nothing to do but to look after their own domestic establishments. They have usually enjoyed excellent health, most of them having had no serious illness since youth, rheumatic fever and rheumatism being the commonest diseases from which they have suffered.

In short, the ensemble of facts relative to the life-history of cancer patients shows, that they have almost invariably led regular, sober, and industrious lives. Persons of drunken and dissolute habits are comparatively seldom affected. In the course of my investigations into the life-history of female cancer patients, I have been much struck by the extreme rarity with which signs of syphilis etc. are met with in such persons.

Thus, of 325 female cancer patients consecutively under my observation, not a single one had ever been addicted to prostitution, so far as I could ascertain ; and, what is still more remarkable, only a single one presented undoubted signs of having had syphilis.

The marked fecundity of these cancer patients, and the rarity of sterility and abortion among them, all point in the same direction ; for sterility and abortion are of frequent occurrence in prostitutes and the syphilitic.

Considerations of this kind negative the doctrine of cancer being *morbus miseriæ.* They point to the greater prevalency of the disease among the well-to-do and easy-going, who habitually eat more than is good for them. Such influences as are comprised under the terms "alimentation" and "domestication," seem to me to be of paramount importance in the ætiology of cancer.

## Scotland.

For the last half-century the Scotch and English cancer death-rates have been singularly alike ; and they have increased *pari passu,* the Scotch figures generally being slightly in excess of their English counterparts as follows :

| | Cancer Death-rate per Million Living. |
|---|---|
| 1861 to 1870 | 416 |
| 1871 „ 1880 | 486 |
| 1881 „ 1890 | 578 |
| 1891 „ 1900 | 739 |
| 1900 | 800 |
| 1901 | 820 |
| 1902 | 830 |
| 1903 | 840 |
| 1904 | 850 |
| 1905 | 890 |

In Scotland, as in England, the increase of the disease has affected both sexes, the corresponding death-rates of each sex in the two countries, being very much alike; but the disproportionate increase among males, is less marked in the Scotch than in the English returns. The Scotch figures are as follows:

| | Male Cancer Death-rate. | Female Cancer Death-rate. |
|---|---|---|
| 1881 | 390 | 630 |
| 1885 | 420 | 690 |
| 1890 | 470 | 740 |
| 1895 | 560 | 880 |
| 1900 | 640 | 950 |
| 1901 | 670 | 970 |
| 1902 | 660 | 990 |
| 1903 | 690 | 970 |
| 1904 | 680 | 1020 |
| 1905 | 700 | 1070 |

The increase of cancer in Scotland, has been accompanied by the same concomitants as in England—that is to say, by diminution of the mortality from tubercle and zymotics, decline of the general death-rate, progressive population, and other signs of material prosperity; while, at the same time, insanity, suicide, etc., have increased.

Thus, the tubercle death-rate declined from 3,600 per million living in 1864, to 2,300 in 1900, and to 2,070 in 1905. In like manner, the death-rate from phthisis, which was 2,220 in 1883, fell to 1,660 in 1900, and to 1,460 in 1903, and these declines have affected both sexes.

As in England, these concomitants have coincided with urbanization, and great increase of material prosperity.

With regard to the former, in 1801, 16·8 per cent. of the Scotch population was urban; in 1851 this percentage had increased to 26·9; and in 1902 to 75·3. The environmental change has, therefore, been almost as complete and abrupt as in England.

With regard to the latter, the proportionate increase in wealth and wages has been nearly as great in Scotland as in England; and it has likewise been accompanied by abundance of food and improved sanitation, whereby the depressing and disease-producing tendencies of urbanization have been combated.

As evidence of this, the decline of pauperism may be instanced—viz., from 4·1 per cent. in 1869 to 2·3 per cent. in 1903.

During the last half-century the wealth of Scotland has enormously increased; and, next to England, Scotland now is one of the wealthiest countries in the world, the average wealth per inhabitant having been estimated at £260 by Mulhall in 1896, as against £330 for England.

With this change, the dietary habits of the people have also been radically altered. Porridge is no longer the staple food as formerly; meat has now taken its place, especially in the towns. Thus, the meat consumption of Scotland in 1895, has been estimated at 180,000 tons per annum; whereas that of Ireland only amounted to 80,000 tons, although its population then exceeded that of Scotland.

It accords with the foregoing, that cancer is found to be least prevalent in the islands of Scotland (56 per 100,000 living in 1900), where the people are poor and the diet is mainly vegetarian ; and it is just in these localities, notwithstanding the rural conditions of existence, that phthisis is most prevalent (182 per 100,000 living in 1900).

Similar conditions prevail in the Shetland Islands.

With regard to the capital, the cancer death-rate of Edinburgh maintains a higher average than that for any other town ; and the rate has increased from 81 per 100,000 living in 1881, to 97 in 1891, to 109 in 1901, and to 135 in 1905 ; while, at the same time, the tubercle mortality has declined, the death-rate for phthisis now being very low.

In the principal towns similar changes have taken place. Thus, while the cancer death-rate for these increased from 70 per 100,000 living in 1891, to 86 in 1902; the phthisis death-rate declined from 218 in the former period, to 161 in the latter.

Among the large towns, Glasgow, where the stress of life is considerable, has long been remarkable for its comparatively low average cancer mortality, coeval with a high death-rate from phthisis ; but with the improving conditions of existence for the masses in comparatively recent times, the cancer mortality has steadily increased, while that from phthisis has decreased. Thus, the cancer death-rate has augmented from 60 per 100,000 living in 1891, to 85 in 1902 ; and the phthisis mortality has decreased from 243 the former year, to 177 in the latter.

In like manner, the county of Berwick, with the highest cancer death-rate in Scotland, has an exceptionally low phthisis mortality.

Thus, in Scotland, as in England, it is evident that the increasing incidence of cancer goes hand-in-hand with diminishing incidence of tuberculous and zymotic maladies, with decline of the general mortality, progressive population, and increased material prosperity, of which the determining factors are to be found in those great changes wrought in the habits and mode of life of the people, by industrialism and urbanization, as I have previously indicated.

## Ireland.

The vital statistics of Ireland during the last sixty years, have been so perturbed by the constant diminution of population, owing to emigration *en masse*, with the consequent reduction in numbers by nearly one-half ; that, in their crude state, they are only available in a certain general way, for comparison with the corresponding English and Scotch data, derived from progressive populations, which have nearly doubled their numbers in the same period. In consequence of this disturbing factor, the Irish population contains fewer children and young adults, but more elderly persons, especially females, than either the English or Scotch populations, and its average age is much higher. The resultant effect of these perturbing influences, has been to exaggerate the ostensible cancer death-rate of Ireland, as compared with that of England and Scotland. Even so, however, the crude cancer death-rate of Ireland, is much less than that of either of the sister communities ; and during the last half-century, its comparative rate of increase has also been rather less. Thus, the Irish cancer death-rate increased from 27 per 100,000 living in 1864 (when registration first came into force), to 61 in 1900, to 65 in 1901, to 67 in 1903, and to 79·3 in 1906, the figures for intervening years being 33 in 1870, 34 in 1880, 39 in 1885, 46 in 1890, and 50 in 1895.

The highest cancer death-rate is found in well-to-do, prosperous Armagh (104); and the lowest in poverty-stricken Kerry (26).

In Ireland, as in England, more women die from cancer than men, the numbers for 1906 being 1,566 males and 1,915 females. The increase of the disease has likewise affected both sexes, but with undue incidence on males.

Pauperism and insanity are more prevalent in Ireland, than in any other division of the United Kingdom; and they are both on the increase.

The prevalence of tubercle in Ireland, moreover, shows no such tendency to diminution as in England. Indeed, the mortality from this cause slightly increased during the latter part of the nineteenth century —viz., from 260 per 100,000 living in 1871-1880, to 290 in 1897-1900; and it is the same with regard to phthisis, the death-rate having increased from 192 in 1871, to 203 in 1906, after having been stationary for several years.

Although Ireland is a very much poorer country than England, and although its material prosperity has, during the last half-century, augmented much more slowly than that of England; yet, as Dr. Grimshaw has shown,[1] its aggregate wealth has steadily increased, notwithstanding the decrease of population and the poverty of the bulk of the people. This result is mainly due to the growth of manufacturing and industrial enterprises in a few localities—*e.g.*, in Ulster, in Dublin and its vicinity, and in Carlow, for which the community is mainly indebted to persons of Anglo-Scotch descent, who are numerous in these localities. Now, it is just in these places that the highest cancer death-rates are found. For instance, Ulster, the seat of the great linen and other industries, had a cancer death-rate of 77 in 1901, which is much above the average; while its phthisis death-rate was 210.

Moreover, it is mainly owing to augmentation of the disease in these localities, that the increased cancer mortality of Ireland, as a whole, is due.

In almost all other parts of Ireland, where rural conditions of existence prevail, and the bulk of the people are decidedly poor and ill-fed, as compared with their English compatriots, cancer is comparatively rare, while tubercle is very prevalent.

### Switzerland.

There are no official statistics relating to the causes of death for the whole country; but, according to Nencki's research,[2] which is based on the cantonal reports, cancer is more prevalent in Switzerland than in any other country, the death-rate from this cause having augmented from 114 in 1889, to 132 per 100,000 living in 1898. This high cancer

[1] Report of the Commission on the Financial Relations of England and Ireland, 1894.
[2] "Die Frequenz und Verteilung des Krebses in der Schweiz," etc., *Zeits. f. schw. Statistik*, 1900, vol. ii., p. 332.

mortality is associated with the comparatively low phthisis death-rate of 189.

During the same period tubercle has steadily declined, the phthisis death-rate having fallen from 234 in 1876-1880, to 187 in 1901.

Three-fourths of Switzerland is mountainous, comprising large areas of forests. The proportion of town-dwellers is a quarter, and it is increasing. Of its 1,500,000 workers, two-thirds are engaged in industrial and commercial occupations, and only one-third in agriculture.

About two-thirds of the people are of German descent, the remainder being of French and Italian origin.

Half a century ago, Switzerland was an exceedingly poor country; now it is one of the most prosperous and well-to-do communities in Europe, the average wealth per inhabitant being £165, or £8 more than in Germany (Mulhall).

There are no millionaires in Switzerland, and no paupers; so that prosperity is even more widely diffused than in France.

The population has been steadily progressive, with a diminishing general death-rate; and the meat consumption is considerable (85 pounds per head per year in 1895).

The cancer mortality varies greatly in the different cantons—viz., from 204 per 100,000 living in wealthy Lucerne, to 36 in poverty-stricken Valais.

### Denmark.

Next to Switzerland, Denmark is reputed to have the highest cancer death-rate of any country in Europe—viz., 130 per 100,000 living in 1900; but statistical data are available only for the towns, the inhabitants of which comprise but a quarter of the entire population; so that the figure for the whole country, although high, would be considerably less than the above.

In these same towns, with this high cancer mortality, we find associated the very low phthisis death-rate of 150.

In 1886-1887 the cancer death-rate of the Danish towns was 109, so that considerable increase has since taken place. During the same period the incidence of phthisis has markedly declined—viz., from about 300 in 1870-1874, to 150 in 1900.

Denmark is an agricultural country whose population, notwithstanding the absence of any great development of manufacturing industries, has nevertheless in a comparatively brief period, experienced a sudden change from serfdom and poverty, to freedom and great prosperity. Serfdom was only abolished at the end of the eighteenth century; and since then these emancipated serfs have largely become yeomen proprietors of their small holdings; so that, in 1890, 71,000 peasant proprietors owned four-fifths of the total soil. Their present state of prosperity is well indicated by the fact that: "the ratio of wealth per head of the population is now higher than in any other country of Continental Europe, except France" (Mulhall).

The only large city in Denmark is Copenhagen, whose inhabitants total one-sixth of the entire population.

The cultivated area is proportionally larger than that of other European countries, and there are but few forests.

Denmark produces hardly any coal or minerals, so that manufacturing industries are much less dominant than in most modern communities.

### France.

In dealing with French vital statistics, due allowance must be made for the fact that they relate only to the towns, which comprise a population of about 12,000,000 out of a total of nearly 39,000,000.

These data show that cancer[1] is very prevalent, and that the incidence of the malady is increasing.

For Paris, the following figures[2] indicate the cancer death-rates: 1865, 84; 1870, 91; 1880, 94; 1890, 108; and 1900, 120.

For all towns of above 10,000 inhabitants (omitting Paris), the figures are: 1887, 76; 1890, 91; 1895, 100; and 1900, 106.

The lowest cancer death-rates are found along the Mediterranean littoral (Corsica, 32 etc.) and in Brittany (Finisterre, 38), where the people are comparatively poor; and the highest are in prosperous Normandy and the adjacent departments (Rouen, 173; Eure-et-Loire, 167 etc.).

The French population, although still predominantly rural, has undergone much urbanization, the ratio of urban to rural inhabitants having increased from 24 in 1846 to 43 in 1900; and this change is almost entirely due to the disproportionate growth of the large towns—*e.g.*, Paris, Lyons, Marseilles, Lille, Bordeaux etc.

The tubercle mortality of the towns is high; and although Paris (439 in 1887, to 394 in 1901), and some of the largest cities, show improvement in this respect, in other towns the decline is but slight. The phthisis mortality for all the towns, which was 245 in 1877, had declined to 213 in 1903.

Next to England, France is the richest country in Europe, and its wealth has been steadily increasing throughout the last century; but the wealth of France is much more widely diffused than that of England. Thus, while the working classes in the two countries number about the same, the French workers own 4,330 millions worth of property, against only 566 for their English compeers. The riches of France are, as it were, clotted in the large towns; and these, as I have previously indicated, everywhere have a higher cancer mortality than the small towns, *chefs-lieux d'arrondissement* etc.

### Sweden.

As in other Scandinavian countries, the cancer mortality of Sweden is high. Statistics exist only for the towns, of which but two (Stockholm and Gottenburg) contain more than 100,000 inhabitants. The urban population comprises about one-fifth of the total inhabitants.

[1] "Cancer et autres tumeurs."

[2] For these data I am indebted to Dr. J. Bertillon; see also his annual publications in the "Annuaire Statistique de la ville de Paris," and for the other towns the "Annuaire Statistique Sanitaire des villes de France," etc.

Judged by death-rates, the Swedes are one of the healthiest races in the world, for their general death-rate during the last decade was only 16·4, the corresponding figures for Norway and England, the next best on the list, being 16·9 and 18·8 respectively.

According to Quensel, there was progressive increase in the mortality from cancer during the last quarter of the nineteenth century—viz., from 80 per 100,000 inhabitants in 1875-1879, to 97 in 1895-1899. In the former period the deaths from cancer amounted to 3·37 of the total mortality; in the latter to 6·27. In 1900, the cancer death-rate had increased to 102. To this increase men have contributed more than women, the sex ratios, which in 1875-1879 were 100 males to 192 females, having changed to 100 to 150 in 1895-1899.

Tubercle is very much less prevalent in Sweden than in most European countries, and the mortality from this cause has declined. Thus, the phthisis death-rate for the towns, which was 280 in 1886-1887, in 1900 had fallen to 170.

A curious feature revealed by Quensel's research is, that the cancer death-rate of the small towns exceeded that of the large ones. Thus, the rate for communities of less than 2,000 inhabitants was 100; for those of from 2,000 to 10,000, 90; and for those of over 10,000 inhabitants, 85.

As previously mentioned, this anomaly, taken with other similar indications, seems to show that the incidence of cancer is determined more by local conditions of existence, than it is by urban or rural life *per se*.

The average consumption of flesh food per head per year is only 67 pounds (Mulhall); but the Scandinavians rely for their proteids quite as much on milk, cheese, and fish, of which immense quantities are consumed, as they do on meat. From what I have myself seen of the dietetic habits of the Scandinavians, I have come to the conclusion that their consumption of proteids exceeds that of most European nations.

### Norway.

In Norway, the population is even more predominantly rural than in Sweden; and, besides agriculture, the lumber trade, fishing, commerce, and cattle-rearing, are their chief resources.

The Norwegian statistics, unlike those of Sweden, apply to the whole population; and they show steady increase in the cancer mortality. Thus, in 1880, the rate was 43; in 1890, 61; and in 1900, 92. The tubercle mortality is almost as low as that of Sweden. The highest cancer mortality is met with in the centres of the fishing, shipping, and timber industries, where the people are financially the most prosperous.

### Holland.

This country, which consists of a fertile alluvial plain traversed by rivers and canals, is noted for its prosperity, which is largely due to agriculture. The cancer mortality is high and increasing. In 1867-1879 the cancer death-rate was 49; in 1884-1888, 66; in 1890, 79; in 1900, 93; in 1903, 99; and in 1905, 101. Its tubercle mortality is decidedly low—viz., about 180—while in 1903 the death-rate from phthisis was only 132, and both are declining.

The lowest cancer death-rate (77) is in the comparatively poor and unproductive province of Drenthe, where large pauper colonies have been established.

In Amsterdam, the cancer mortality increased from 38 in 1891, to 78 in 1900; while the death-rate from phthisis fell from 260 in 1862-1863, to 177 in 1897-1901.

## Germany.

According to Maeder[1] and Wutzdorff,[2] whose researches are based upon official data,[3] cancer has of late increased in Germany, while tubercle has declined; and these changes have coincided with increased general prosperity.

The cancer death-rate, which was 59 in 1872, increased to 71 in 1900. *Per contra*, the tubercle mortality has declined 38 per cent. since 1875.

In Berlin, the cancer rate increased from 57 in 1870-1882, to 109 in 1899; while phthisis declined from 310 in 1876, to 190 in 1901.

The Hamburg cancer rate increased from 71 in 1872, to 97 in 1898. During the same period, the mortality from phthisis declined from 340 in the former year to 194, in the latter; and there was also marked diminution in the general death-rate.

Of the constituent States of Germany, the rich southern ones have much the highest cancer death-rates.

*Baden* heads the list (101), and, as Maeder has shown, the disease has increased there.

*Bavaria* comes next, with an increase from 56 in 1880, to 98 in 1900. In Munich the increase was from 88 in 1890, to 119 in 1900.

In *Saxony*, the increase has been from 69 in 1876-1885, to 95 in 1900. During about the same period phthisis declined from 231 (1873-1875), to 190. Of late, the high Dresden cancer rate has been about stationary—viz., 123 in 1891, and 125 in 1900.

In Stuttgart, the cancer death-rate increased from 76 in 1891, to 127 in 1900.

The average cancer mortality in *Prussia* is much less than that of these southern States, but even here the disease has increased—viz., from 31 in 1881, to 59 in 1900, and to 60 in 1905. The phthisis death-rate has declined from 360 in 1851, to 150 in 1901; but insanity has notably increased.

Cancer is probably more prevalent in Schleswig-Holstein (76), where Danish conditions of existence prevail, than in any other division of Prussia; and the Kiel rate (113), is higher than that of any Prussian town.

[1] *Zeits. f. Hygiene*, etc., Bd. xxxiii., 1900, S. 235.
[2] *Deutsche med. Woch.*, March 6, 1902.
[3] "Medizinal-Stat. Mittheil., aus den k. Gesundheitsamte."

It is least prevalent in the provinces bordering on Poland—Posen (44), East Prussia (54), West Prussia (50), and Silesia (54)—where the working classes are poor, comprising many Poles and Jews.

### Austria.

In this country the cancer mortality has increased from 37 in 1880, to 70 in 1900; and coincidently there has been a great decline in the death-rates from phthisis and all kinds of tuberculosis. The tubercle rate is, however, still high—viz., 349 for phthisis in 1903.

The highest cancer death-rates are met with in the prosperous and well-to-do provinces of Salzburg (133), Upper Austria (115), Lower Austria (108), Tyrol and Vorarlberg (107) etc.; and the lowest in the poor provinces of Bukowina (37), Galicia (28), and Dalmatia (19). In Bukowina and Galicia, Polish Jews comprise a large proportion of the population, and in Dalmatia there is a large Italian element.

In Vienna the cancer rate increased from 107 in 1875, to 121 in 1900. With regard to tubercle, the mortality declined from 763 in 1872-1876, to 467 in 1897-1900.

### Hungary.

As compared with Austria, Hungary is a poor country, with the phenomenally low cancer death-rate of 33, which in 1897 was only 26, and in 1903 it reached 39. The tubercle mortality of Hungary is the highest in Europe—viz., 387 in 1903.

The Buda-Pest cancer rate increased from 62 in 1896, to 72 in 1900, and the tubercle mortality has declined of late.

### Italy.

Cancer is much less prevalent in Italy, which is a comparatively poor country, than in most European communities; but even here the mortality has increased from 21 in 1880, to 52 in 1899, and to 58 in 1905.

The tubercle death-rate is diminishing, but to a less extent than in most European countries, having fallen from 122 in the period 1897-1904, to 118 in 1905.

The meat consumption per head (23 pounds in 1895) is the smallest of any European nation.

The highest cancer rates are met with in the prosperous and well-to-do provinces of the north—Tuscany (83), Emilia (78), Lombardy (71) etc.—and it is here that the diminution in the tubercle mortality has been most marked. The lowest cancer rates are in the comparatively poor provinces of Apulia, Basilicata, and Calabria (30), while for Sardinia the phenomenally low rate of 19 is registered.

For the chief towns the cancer rates are as follows: Florence, 137; Ravenna, 120; Milan, 101; Venice, 103; Rome, 77; Turin and Genoa, 59; and Naples, 56.

### United States.

With regard to extra-European countries, data are available for the United States, Australia, and New Zealand.

In what follows in this section the reservation previously made, with regard to the peculiar difficulties under which vital statistics are compiled in the United States, must be borne in mind.

Such data as are forthcoming for the whole community show that the mortality from cancer and tumour increased from 9 per 100,000 living in 1850, to 29 in 1880, to 33 in 1890, and to 43 in 1900. The proportion of deaths from this cause to 1,000 deaths from all causes, increased from 25·4 in 1890, to 32·9 in 1900.

In the "registration area" alone, the "cancer and tumour" death-rate increased from 53 in 1890, to 65 in 1900.

In the same limited area, the death-rate from cancer alone, increased from 47 in 1890, to 60 in 1900.

There is no need to dilate upon the great increase in the riches, prosperity, and population of the United States during the nineteenth century, although it may here be remarked that, as in England, the wealth of the community is much less widely diffused among the population than in France, Switzerland, Denmark, and some other countries.

Although urbanization has made great progress in the United States, the towns of 8,000 inhabitants and upwards having increased from 6 in 1790, to 546 in 1900, nevertheless, two-thirds of the population still dwell in the country, and are mainly dependent upon agriculture.

A diminishing tubercle death-rate has coincided with the increase of cancer, the tubercle rate having fallen from 245 in 1890, to 187 in 1900.

The meat consumption of the United States population, is considerably in excess of the European average.

Cancer is much more prevalent in the northern than in the southern part of the United States, the chief centres being the wealthy commercial States of the Atlantic coast and vicinity (51 to 41) and the Pacific States (51). The lowest rates are in the South Mississippi River belt (11), the south-west central region (15), the southern interior plateau (18) etc. It is in these southern localities that the negro race is chiefly comprised; and their cancer death-rate (47) is lower than that of the whites (66); but, even in southern States where negroes are rarely found, the cancer rates are very much below the average.

For some of the chief cities of the United States, the following increases in the cancer death-rates have been recorded: New York, from 32 (1864) to 67 (1900); Chicago, from 32 (1880) to 63 (1900); Philadelphia, from 31 (1861) to 70 (1904); Boston, from 28 (1863) to 85 (1903); Baltimore, from 18 (1864) to 63 (1903); New Orleans, from 15 (1864) to 82 (1903); and San Francisco, from 16 (1866) to 112 (1900).

**Australia.**

Thanks to the valuable publications of Adams,[1] Allen,[2] Mullins,[3] Coghlan,[4] etc., we have fairly complete information as to the incidence of cancer in Australia during the last half-century. These data show steady increase of the disease, the death-rate per 100,000 living having been as follows: 14 (1851), 19 (1861), 25 (1871), 32 (1881), 45 (1891), and 57 (1901).

Males have been relatively affected by this increase more than females. Thus, during the period 1870-1900, the male rate increased from 26 to 59, whereas the augmentation for females was from 28 to 55 (Allen). A remarkable fact revealed by these data is, that the male cancer death-rate now exceeds the female rate; and this holds as well for each of the constituent communities, as for the whole commonwealth.

Some conception may be formed, as to the conditions of existence during the period to which these data refer, from the fact that it has been characterized by great increase and wide diffusion of material prosperity, by diminution of the tubercle and general mortality, by increase of insanity, by lessened birth-rate, by excessive consumption of meat, and by disproportionate increase of the capital towns.

For the different divisions of the Australian Commonwealth, the following progressive increases in the cancer rates have been recorded:

*New South Wales:* 28 (1871-1875), 51 (1894), 57 (1900), and 65 (1903). For males, the rate increased from 18 (1860-1864) to 51 (1895-1899); and, for females, from 21 (1860-1864) to 50 (1895-1899).

The phthisis death-rate declined from 92 (1871-1875) to 79 (1896-1898).

*Victoria:* 32 (1871-1875), 61 (1891-1895), 72 (1900), and 76 (1903).

The phthisis rate was 120 (1871-1875), 123 (1896-1898), and 111 (1903).

*Queensland:* 17 (1871-1875), 35 (1891-1895), 46 (1900), and 49 (1903).

The phthisis rate declined from 109 (1871-1875) to 93 (1896-1908), and to 78 (1903).

*South Australia:* 20 (1871-1875), 47 (1891-1895), 59 (1900), and 72 (1903).

The phthisis rate was 89 (1871-1875), 87 (1896-1898), and 75 (1905).

*West Australia:* 15 (1871-1875), 30 (1891-1895), 32 (1898), and 40 (1905).

The phthisis rate declined from 85 (1871-1875) to 75 (1896-1898), and to 65 (1905).

*Tasmania:* 48 (1871-1875), 49 (1891-1895), 60 (1900).

The phthisis rate declined from 101 (1871-1875) to 73 (1896-1898).

While the average cancer death-rate for all Australia was 57 in 1900, or 5 per cent. of the total mortality from all causes, in the capital cities the cancer death-rate was 81, or 6·4 per cent. of the total mortality;

[1] *Lancet*, 1904, vol. i., pp. 423, 498.
[2] *Australian Medical Gazette*, April 21, 1902, p. 169.
[3] *Ibid.*, January 20, 1896.
[4] *Ibid.*, April 21, 1902, p. 174; see also his "Wealth and Progress of New South Wales," 1894.

whereas, in the rural districts, the cancer rate was only 44, or 3·9 per cent. of the total deaths from all causes.

I have previously referred to the greatly increased proclivity to cancer experienced by British immigrants in Australia, of which the latest Australian vital statistics afford some striking evidence. Thus, for 1900, while the cancer death-rate of native-born Australians was only 22, the corresponding rate for the British-born was 203 ; and, for other foreign-born persons, as follows : French, 375 ; Austrian, 300 ; Scandinavian, 289 ; and German, 252. In 1895, Mullins found that of the British-born, in Australia, 1 in 966 died of cancer, as against 1 in 7,746 of the native-born white Australians. These rates are much in excess of those prevalent in the immigrants' native countries.

Even when the figures have been corrected for age differences, the same result is shown ; for, taking persons aged thirty-five years and upwards, 58 per 100,000 living of the Australian-born died of cancer, as against 137 of the British and foreign-born.

Dr. MacDonald, of Dunedin, believes that this proclivity is mainly due to the gluttonous habits of the immigrants in respect to meat-eating : "Meat for breakfast, lunch, dinner, tea, and supper, just like the porridge-pot in Scotland."

Even the Chinese in Australia suffer severely from cancer, for their mortality from this cause, in 1900, amounted to 72 per 100,000 ; and of 1,316 Chinese deaths registered in Victoria in 1894-1900, 42 were due to this malady.

With regard to the Australian aborigines, however, who in 1891 numbered about 60,000, Allen notes : that "cancer is rare among them, many years often passing without a single case being registered, although they are not really exempt from either external or internal cancer."

Among the Pacific Islanders, employed in Queensland, Roth reports that, during the last eleven years, he has never seen or heard of a single case of cancer ; and several other medical men have testified to the same effect.

### New Zealand.

In these islands the conditions of existence much resemble those current in Australia ; and the proclivity to cancer is much the same in the two countries, the New Zealand rate having increased from 32 (1877-1888), to 44 (1891), to 60 (1900), and to 71 (1903). Taking 100 as the standard, the cancer mortality for males in the last twenty years increased to 367, as against 260 for females. The phthisis rate declined from 87 (1871-1875), to 75 (1900), and to 69 (1903). In New Zealand, as in Australia, the birth-rate and the general mortality have declined, while insanity has increased. British immigrants are much more prone to cancer, than the native-born white New Zealander ; but, the aborigines are seldom affected.

# CHAPTER IV

## THE TOPOGRAPHICAL DISTRIBUTION OF CANCER

In every part of the world the incidence of cancer presents well-marked topographical variations, to many of which I have referred in the foregoing chapters; but the importance of the subject seems to demand more detailed consideration.

C. H. Moore[1] was the first to study these variations for England and Wales. He showed that the disease was more prevalent in London and its vicinity, in the southern and eastern counties, than elsewhere; and that it was least prevalent in the north-western and northern counties, and in Wales. If, he says, the country be divided by a line drawn from Bristol to Peterborough, the mortality from cancer in the southern divisions is considerably in excess of that on the north of the line. In the year 1861, for instance, one of every thirty deaths of females in the south-eastern division was due to cancer; while in the north-western division, the proportion was only 1 to 59, or about one-half. Moore gives the following instructive data (see table, p. 80).

Some years later the same subject was thoroughly reinvestigated, with due allowance for diversities in age and sex distribution, by Haviland,[2] and Moore's results were in every respect confirmed.

The districts having the highest cancer mortality (4 to 6 per 10,000 living) comprised London, the south-eastern and eastern counties; those with the lowest mortality (3 to under 2 per 10,000 living) were the north-western counties, Monmouth, and Wales; between these extremes were the northern, midland, and south-western counties, with a cancer death-rate of from 3 to 4 per 10,000 living.

These investigations comprised the decennia 1851-1860 and 1861-1870; and, although in the intervening period, the cancer mortality was shown to have everywhere increased, yet those localities having the highest, lowest, and medium cancer rates were the same for both periods.

In the Forty-seventh Annual Report of the Registrar-General, this subject received official attention. The subjoined table (see p. 81) from this source, shows the mean annual cancer mortality per standard million

[1] "Antecedents of Cancer," London, 1865, p. 41.
[2] "Geographical Distribution of Disease in Great Britain," 2nd edit., 1892; 1st edit., 1875.

| Divisions. | 1851. | | | | 1861. | | | | 1851-1860. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | One Cancer Death to Population. | | One to Total Deaths. | | One Cancer Death to Population. | | One to Total Deaths. | | One Death from Cancer in Females aged 35 to 64. | One Death from Cancer in Total Female Mortality between Ages 35 to 64. |
| | Male. | Female. | Male. | Female. | Male. | Female. | Male. | Female. | | |
| London .. | 4884 | 1778 | 113 | 38 | 3758 | 1553 | 95 | 34 | 67 | 12 |
| S.-Eastern: (Surrey, Kent, Sussex, Hampshire, Berkshire) | 5362 | 2206 | 105 | 41 | 4419 | 1697 | 86 | 30 | 83 | 12 |
| South-Midland: (Middlesex, Herts, Bucks, Oxfordshire, Northampton, Huntingdonshire, Beds, Cambridgeshire) | 4304 | 2163 | 87 | 42 | 3520 | 2141 | 72 | 41 | 89 | 13 |
| Eastern: (Essex, Sussex, Norfolk) | 7226 | 2131 | 150 | 42 | 4553 | 1713 | 98 | 34 | 84 | 12 |
| S.-Western: (Wilts, Dorset, Devon, Somerset, Cornwall) | 4921 | 2343 | 103 | 45 | 4309 | 1920 | 85 | 34 | 100 | 14 |
| W.-Midland: (Gloucestershire, Herefordshire, Shropshire, Staffordshire, Worcestershire, Warwickshire) | 7478 | 2470 | 177 | 55 | 5057 | 2175 | 109 | 42 | 90 | 14 |
| N.-Midland: (Leicestershire, Rutland, Lincs, Notts, Derbyshire) | 6417 | 2692 | 131 | 54 | 4499 | 2329 | 96 | 47 | 97 | 14 |
| N.-Western: (Lancashire, Cheshire) | 7946 | 3263 | 214 | 80 | 6249 | 2454 | 166 | 59 | 103 | 20 |
| Yorkshire: (West, East, and North Ridings) | 5881 | 2869 | 141 | 65 | 4634 | 3068 | 110 | 45 | 100 | 16 |
| Northern: (Durham, Northumberland, Cumberland, Westmorland) | 5454 | 2970 | 119 | 60 | 3983 | 2258 | 92 | 49 | 102 | 16 |
| Wales: (North, South, and Monmouthshire) | 7166 | 3833 | 149 | 74 | 4282 | 2962 | 92 | 59 | 137 | 20 |
| England and Wales | 5846 | 2461 | 133 | 52 | 4484 | 2019 | 101 | 41 | 91 | 15 |

aged twenty-five and upwards, in the registration divisions during the thirty years 1851-1880 :

| | Males. | Females. | Persons. |
|---|---|---|---|
| London .. .. .. .. .. .. | 736 | 1463 | 1117 |
| South-Eastern .. .. .. .. .. | 557 | 1207 | 898 |
| South-Midland .. .. .. .. .. | 597 | 1148 | 886 |
| Eastern .. .. .. .. .. .. | 502 | 1175 | 855 |
| West-Midland .. .. .. .. .. | 519 | 1133 | 841 |
| Yorkshire .. .. .. .. .. | 511 | 1114 | 827 |
| Northern .. .. .. .. .. | 565 | 1041 | 815 |
| South-Western .. .. .. .. .. | 555 | 1043 | 811 |
| North-Western .. .. .. .. .. | 523 | 1055 | 802 |
| North-Midland .. .. .. .. .. | 496 | 1074 | 799 |
| Wales . .. .. .. .. .. .. | 538 | 841 | 697 |
| England and Wales (average) .. .. | 561 | 1444 | 867 |

It will be seen that the results brought out by this table, are practically identified with those previously elicited by Moore and Haviland.

In the supplement of the Fifty-fifth Annual Report of the Registrar-General, a somewhat similar table for the counties is given for the decennium 1881-1890 [1]; but, in this case, the mortality is for persons aged thirty-five years and upwards.

The counties with the highest rates were :

| | Males. | Females. | Persons. |
|---|---|---|---|
| London .. .. .. .. .. | 1784 | 2667 | 2250 |
| Huntingdonshire .. .. .. .. | 1916 | 2373 | 2157 |
| Cambridgeshire .. .. .. .. | 1666 | 2323 | 2012 |
| Sussex .. .. .. .. .. | 1491 | 2454 | 1999 |
| Warwickshire .. .. .. .. | 1533 | 2373 | 1976 |

Those with the lowest rates were :

| | Males. | Females. | Persons. |
|---|---|---|---|
| Lancashire .. .. .. .. .. | 1275 | 2092 | 1706 |
| Durham .. .. .. .. .. | 1227 | 2117 | 1696 |
| Staffordshire .. .. .. .. .. | 1234 | 2048 | 1663 |
| Rutlandshire .. .. .. .. | 1429 | 1874 | 1663 |
| Worcestershire .. .. .. .. | 1213 | 2048 | 1653 |
| South Wales .. .. .. .. .. | 1352 | 1911 | 1647 |
| Cornwall .. .. .. .. .. | 1380 | 1855 | 1630 |
| Wilts .. .. .. .. .. .. | 1122 | 2036 | 1604 |
| Derbyshire .. .. .. .. .. | 1038 | 2098 | 1597 |
| Buckinghamshire .. .. .. .. | 1129 | 2095 | 1578 |
| Dorsetshire .. .. .. .. .. | 1143 | 1967 | 1578 |
| Monmouthshire .. .. .. .. | 1157 | 1948 | 1574 |
| England and Wales (average) .. .. | 1397 | 2261 | 1844 |

[1] In the preceding decennium (1871-1880) the highest cancer rates for persons aged twenty-five years and upwards were in London (1269), Cambridgeshire (1193), Northamptonshire (1138), Huntingdonshire (1138), Sussex (1137), and Warwickshire (1095); and the lowest rates were in Lancashire (944), North Wales (933), Dorset (929), Monmouthshire (925), Cornwall (917), Durham (898), Hertfordshire (895), Buckinghamshire (881), South Wales (873), and Derbyshire (839).

The highest and lowest death-rates for *all ages*—corrected for age and sex distribution—for the same decennium, were met with in the following counties:—the highest were in Huntingdonshire (916), Cambridgeshire (789), Devonshire (786), North Wales (736), Sussex (727), Norfolk (716), London (683); and the lowest were South Wales (501), Monmouthshire (482), Derbyshire (482), Lancashire (477), Staffordshire (475), and Durham (440).

In the registration divisions, the cancer death-rates per million living of all ages and both sexes, in 1884, and in 1900, were as follows:

| | 1884. | 1900. |
|---|---|---|
| London | 650 | 964 |
| South-Eastern | 622 | 883 |
| South-Midland | 694 | 929 |
| Eastern | 763 | 895 |
| West-Midland | 595 | 863 |
| Yorkshire | 536 | 809 |
| Northern | 442 | 816 |
| South-Western | 642 | 950 |
| North-Western | 490 | 773 |
| North-Midland | 520 | 798 |
| Wales | 533 | 775 |
| England and Wales (average) | 560 | 828 |

In the counties, the highest and lowest rates per million living at all ages for 1890, 1900, and 1901 were as follows:

| | 1890. Both Sexes. | 1900. Both Sexes. | 1901. Males. | 1901. Females. |
|---|---|---|---|---|
| Huntingdonshire | 1108 | 1083 | 964 | 1300 |
| Cambridgeshire | 939 | 1033 | 951 | 1330 |
| North Wales | 871 | 1063 | 981 | 1200 |
| Devonshire | 847 | 964 | 818 | 1121 |
| Norfolk | 781 | 991 | 879 | 1132 |
| Suffolk | 779 | 991 | 790 | 1031 |
| Derbyshire | — | 783 | 519 | 932 |
| South Wales | 563 | 658 | 577 | 798 |
| Lancashire | 555 | 730 | 593 | 905 |
| Staffordshire | 538 | 685 | 482 | 802 |
| Durham | 518 | 619 | 497 | 804 |
| Monmouthshire | 504 | 606 | 576 | 789 |
| England and Wales (average) | 676 | 828 | 691 | 985 |

The general outcome of these data, which cover the whole of the last half of the nineteenth century, is to show the accuracy of Moore's conclusions as to the local incidence of the disease.

Another important indication furnished by them is, that the increase of the disease has involved the whole of the country, in such a manner that those divisions and counties, which formerly had the highest, lowest, and medium cancer rates, for the most part, still retain their peculiarities in these respects, although the incidence of the disease has everywhere augmented.

But, although the local incidence of the disease is thus shown to be remarkably persistent; yet, in several cases, changes in the comparative proclivity of certain localities have occurred; thus, North Wales, where the cancer mortality was formerly much below the average, is now subject to a high rate; and this change seems to have coincided with the invasion and settlement of the locality by well-to-do immigrants from the large towns of Lancashire and the Midlands, with their industrial, wealth-producing innovations etc.

The foregoing data refer exclusively to the death-places of cancer patients, which, of course, may not correspond with their birth-places. By noting the birth-places of 352 cancer patients, I was able to ascertain that the localities where the highest cancer mortality obtains, are also the localities where most cancer patients are born—thus confirming Nunn's research on the same subject.[1]

It is a matter of importance to determine the part played in the causation of these local variations in the cancer mortality, by differences in the age and sex distribution of the population; and the Registrar-General has lately published data that enable corrections of this kind to be made. Although the accuracy of the general results indicated by the crude death-rates is not impugned by these corrections, yet the comparative mortality of individual counties *inter se* is often disturbed; thus, while the crude cancer death-rate of Huntingdonshire to that of Durham (1881-1890), was as 208 to 100, the corrected ratios are as 127 to 100—yet the former county, after correction, still retains its status as one of those districts where cancer is most prevalent, and the latter as one of those where it is least so.

Corrected for age and sex diversities, the counties with the highest cancer rates are London, Huntingdonshire, Cambridgeshire, Sussex, Warwickshire etc.; while those with the lowest rates are Monmouthshire, Derbyshire, Durham, Staffordshire, Lancashire, South Wales, Dorset, Bucks, Wilts, Cornwall etc.

It is thus evident that there are topographical variations in the incidence of cancer, which are quite independent of age and sex diversities; and, it may also be added, of the disturbing influence caused by the presence of large hospitals.

Hence, it is exceedingly improbable that the higher cancer mortality of the agricultural, as compared with the industrial population, can be explained as the result of any of the above-mentioned disturbing factors, although such certainly exist.

In like manner, the average age of the Irish population is much higher than that of either England or Scotland, and the proportion of elderly women it contains is also greater, owing to the large numbers of elderly people left behind after the younger ones have emigrated; yet, the cancer mortality of Ireland is much less than that of either England or Scotland, which clearly shows that inequalities in the incidence of cancer mortality are determined by other considerations besides those of age and sex distribution.

According to Haviland,[2] these variations are entirely due to geological configuration and its consequences.

[1] For further details *vide* my work on "Diseases of the Breast," 1894, p. 256.
[2] *Op. cit.*

He maintains that the regions of highest cancer mortality are low-lying districts, traversed by, or contiguous to, rivers that seasonally flood the adjacent riparial lands; whereas the lowest cancer mortality is found in high and dry sites, where floods do not occur, and where the subsoil consists of hard, non-retentive rocks—*e.g.*, English lake district—or of absorbent substances like chalk and oölite. In support of these views, he instances the Thames and its tributaries, which run through a vast cancer-field; and he points to the only localities in the Thames Valley—the Orsett and Dartford districts—where there is a low cancer mortality, as being just those spots where the chalk crops out.

In favour of the opinion that, in this country, cancer is specially prevalent in flat, low-lying, fenny districts, there is, I think, much to be said. The Forty-seventh Report of the Registrar-General shows that Cambridgeshire and the adjacent counties of Northamptonshire, Huntingdonshire, and Bedfordshire, all have a very high cancer mortality. Lincolnshire and Essex figure less prominently in this Report; but my analyses show that the number of cancer patients born in these localities is exceedingly high. This state of things is known to have existed ever since statistical records have been kept. In the decennial Report (1881-1890), the Registrar-General—writing on this subject—says: "Crude death-rates show that in and around Huntingdonshire and Cambridgeshire, there is a well-defined area in which cancer is exceptionally prevalent. It comprises the districts of Stamford, Bourn, Spalding, and Holbeach in Lincolnshire; Oundle and Peterborough in Northamptonshire; and most of the counties of Huntingdonshire and Cambridgeshire. In 1881-1890 this area had a mean population of over 300,000, its crude cancer rate being 857 per million, or 46 per cent. above the average rate for the country in general; in the preceding decennium the excess was 44 per cent."

Nevertheless, I am unable to accept Haviland's views as a sufficient explanation of the topographical variations in the distribution of cancer. All low-lying and seasonally flooded districts have not a high cancer mortality. The very large area drained by the Severn and its tributaries, for instance, is shown by the Registrar-General's Forty-seventh Report, to have a low average cancer mortality.

Moreover, islands that have no rivers, that are not low-lying, and that are not of alluvial formation, nevertheless have a high cancer mortality; such are the Scilly and Channel Islands, and the Isle of Wight may also be mentioned in this connexion.

The Scillies are small and rocky throughout, their total population being about 2,000; but, during the decennium 1881-1890, their cancer death-rate was considerably higher than that for all England, and still more was it in excess of that for the adjacent mainland (Cornwall).

The cancer death-rate for these islands, per 10,000 living, for the decennium (1881-1890) was 7·6 (males 2·9, females 12·2), the corresponding figures for all England and Wales being 5·8 (males 5·8, and females 7·3).

For the Isle of Wight, the cancer death-rate, in 1900, was 9·4 per 10,000 living, or 1 in 16 of the total mortality.

A Jersey practitioner having informed me that cancer was very prevalent there, as well as in Guernsey, I wrote to the gentleman who furnishes the mortality statistics—such as they are—for Jersey, to the Registrar-General; but failed to elicit a reply.

Similar conditions are met with in many inland districts; thus, Dr. Borrowman, of Elie, in Fifeshire, N.B., writes to me: "It will interest you to know that cancer is very common here. Between 11 and 12 per cent. of my patients have died from malignant disease. This is a particularly dry part of the country. There are no rivers at all in the district; and the few streams that do exist have a good fall. Flooded land is quite unknown here."

In other countries this peculiarity has also been noted; thus, cancer is very prevalent in the Ballarat gold-field region of Victoria, where no rivers, no alluvial valleys, and no malaria occur, the whole country being a volcanic plateau, from which the rain drains away as soon as it has fallen.[1]

Recently attempts have been made by the microbists, to explain these topographical variations as the outcome of contagion; but, the peculiar manner in which this malady is distributed throughout the whole country, and the constancy with which the various local incidence ratios have been maintained from decennium to decennium, notwithstanding the universal increase, tells against this theory, the general inadequacy of which I shall subsequently have occasion to point out.

It appears to me that the explanation of these variations must be sought, in the conditions of life peculiar to the respective populations.

Let us now carefully examine the vital statistics of our country for the last half-century, in order to determine the particular conditions which have tended to this end. Such an examination shows—as I have previously indicated—that the cancer mortality is lowest where the struggle for existence is hardest, the density of population greatest, the tubercle mortality highest, the birth-rate highest, the average duration of life shortest, the infantile and general mortality highest, and where sanitation is least perfect—in short, among the poor of the industrial classes in our large towns; whereas, among the wealthy and well-to-do—where the standard of health is at its best, and life is easiest, and all the conditions of existence are just the converse of the foregoing—and among the agricultural community, there the cancer mortality is highest. Other things being equal, there are, in my opinion, no more potent factors in the causation of cancer than high feeding and easy living. Hence it is that the cancer mortality of mining and industrial centres, like South Wales, Monmouthshire, Lancashire, Durham, Derbyshire, Staffordshire, Cornwall, West Riding, etc., is so low; and that it contrasts so favourably with the cancer mortality of the generality of agricultural districts. Although the ratio of pauperism in the rural districts is quite double that of the industrial ones, I have no hesitation in saying, as the result of my own observation of life under both conditions, that so far as food and comfort are concerned, the average agricultural labourer is much better off during his working years than his confrère of the industrial army. As a proof of this, it may be mentioned that the average duration

[1] J. H. Well, *Lancet*, vol. ii., 1901, p. 976.

of the agricultural labourer's life, is more than double that of his mate in the large towns; and his wages and general conditions of existence have greatly improved during the last half-century. On this subject a leading London newspaper remarked:[1] "The material prosperity of the agricultural labourer is, and has been, during recent years, higher than at any period during the last century. The slight falling-off in the amount of his wages is more than compensated for by their increased purchasing power. All the necessaries of life, during the last thirty years, have become much cheaper—meat, bacon, cheese, tea, sugar, butter, and coal—the difference being something like 25 per cent. in favour of the buyer."

Provincial towns with the highest cancer death-rates per 100,000 living, during the decennium 1881-1890 are:—Chichester (118), Canterbury (113), Bala (107), Huntingdon (106), Exeter (101), Saffron-Walden (99), Cirencester (97), Cambridge (95), St. Asaph (94), Dolgelly (94), Buckingham (94), Bath (93), Scarborough (93), Holbeach (92), Devizes (91), Bury St. Edmunds (90) etc.

It is noteworthy that this list does not include a single great industrial centre, the places named being well-to-do, easy-going, residential country towns.

For the great industrial centres the rates are much less, viz., Bristol (83), Birmingham (72), Liverpool (69), Manchester (67), Leeds (62), Newcastle (55), Derby (52), Sheffield (50), Salford (48), Wolverhampton (47), Cardiff (45), West Ham (40), Bolton (40), Blackburn (38), Durham (32) etc.

In London and its vicinity, where the wealth of the nation is clotted, there the cancer mortality is highest; and it is significant that this mortality is highest of all in those parts of the metropolis and its suburbs, where the well-to-do most abound. Thus, for 1903, the highest cancer rates were in wealthy Hampstead, Marylebone, Chelsea, and Westminster; while the lowest were in the poor industrial districts of Bermondsey, Stepney, Bethnal Green, Poplar, and in the poverty-stricken extra-metropolitan district of West Ham. Crude rates show, that the disease is very much more prevalent in the former than in the latter group of communities. Corrections for age and sex diversities, for hospitals and other public institutions, although they somewhat mitigate these extremes, still show that the cancer mortality is much less in the poor industrial districts, than it is in those inhabited by the wealthy and well-to-do. Moreover, a similar state of things is noticeable in all our large towns (as I have previously indicated in the case of Bristol), and throughout the country in general.

In other European countries, where sufficiently detailed statistics have been kept, similar topographical variations in the incidence of the disease are everywhere noticeable.

[1] *Standard*, August 12, 1897.

# CHAPTER V

## CANCER AND OTHER TUMOURS IN ANIMALS

### Some General Remarks on Tumours in Animals.

CONSIDERING the great advances lately made in most branches of biology, the stagnation of comparative pathology is a surprising and regrettable anomaly; for, many of the most important pathological problems now pending, might be more profitably investigated by this method, than by the experimental or other dispersive analytical procedures, now so much in vogue.

Although progress has lately been made, the comparative pathology of tumours is still in a rudimentary and backward condition.

Some important conclusions have, however, already been established.

Morphological and physiological processes being similar in the animal world and in mankind, it is only reasonable to suppose that pathological processes will also manifest a certain similarity; and, from what is known of the diseases of animals, this supposition appears to be fully justified, at any rate, so far as tumours are concerned, it has been ascertained that the analogy holds good.

In vegetable organisms, physiological and pathological processes are certainly much less complex than in animals, if only in that the former are destitute of nerve and lymph-vascular systems, which add so much to the difficulty of disentangling the genesis of vital processes in the latter.

As I have shown in my book on the "Principles of Cancer and Tumour Formation," which was published in 1888, the really fundamental physiological and pathological processes are the same in plants as in animals; and it accords with this, as I have indicated in the above-mentioned work, that malignant and other tumours also originate in vegetable organisms.

We thus arrive at the important conclusion, that tumours may arise, under certain circumstances, in any multicellular animal or vegetable being.

Another consideration to which I have previously called attention is, that these abnormalities very rarely affect organisms living in a state of nature. It is almost exclusively among domesticated varieties, among those that have been kept long in confinement, or that have been otherwise abnormally circumstanced, that tumours are met with; thus, in savages and wild animals, tumours very rarely occur.

Nearly all of those who have specially studied the comparative incidence of tumours in animals and mankind, are agreed that these maladies are relatively infrequent in the former; and this appears to me to be due to the fact, that animals have been much less extensively subjected to the influence of domestication, and to such other abnormal conditions of existence as I have above referred to, than mankind. At any rate, it is remarkable that nearly all the examples of animal tumours hitherto reported, have been met with in our common domesticated species.

Recent observations as to the relative frequency of malignant tumours in the latter, show that these maladies are not so rare as was formerly believed: thus, Veterinary-Inspector Trotter found that of 47,362 cattle, slaughtered at Glasgow in 1903, 131 had some form of malignant tumour, or 2·8 per 1,000, the corresponding ratio for English humanity being about 60 per 1,000.

All the indications at present available point to the great rarity of cancer in wild animals, whether living in confinement or under natural conditions; indeed, but very few instances of this kind have so far been reported.

Of 2,647 wild mammals comprised in the New York Zoo, during a period of five years, H. Brooks [1] reports that not a single specimen of tumour was met with, although they were specially examined *ad hoc*. A large proportion of these animals had only recently been reduced to captivity. Of those which died, 744 were submitted to thorough post-mortem examination; yet, only a single case of malignant tumour was found, viz., sarcoma of the ovary of a wild, white, racoon-dog (*Nyctereutes albus*), from the north of Japan, which sickened and died emaciated after a sojourn of two years in the Zoo.

Under these circumstances, it seems to me that the dictum of the Cancer Research Fund [2] as to the incidence of cancer in animals approximating in frequency to that in mankind must be rejected, as being without scientific warrant.

In respect to such conditions as the foregoing, there is some analogy between the incidence of tumours and developmental anomalies; for the latter, like tumours, are relatively rare in savages and wild organisms; whereas, they are common in mankind, in domesticated organisms, and in those that have been kept long in confinement, or that have been otherwise abnormally circumstanced.

In this connexion, I must call attention to another noteworthy concomitant of the augmented British cancer mortality, viz., the great increase in the incidence of congenital defects and premature births, as to which I shall subsequently have to refer more in detail.

Thus, whatever the causes of malignant tumours may be, they are not limited to mankind—as John Hunter, Camper, Otto, and some other pathologists believed—nor even to the animal world, as most modern pathologists even now suppose.

From such facts as have already been ascertained with regard to tumours in animals, it may be confidently predicted, that all the varieties

[1] *American Journal of Medical Science*, May, 1907, p. 769.
[2] Scientific Reports of the Imperial Cancer Research Fund, No. 2, part i., 1905.

of the neoplastic process recognized in mankind have their counterparts in the animal world.

It appears to me that the chief feature in which animal tumours differ from their human congeners, is in respect to the relative frequency of site incidence; and this I suspect is mainly the outcome of diversity of function and structure in certain organs, which, in their turn, ultimately depend upon differences in habit and mode of life—for such influences are as potent in pathology, as in physiology.

In the first place, it is noticeable that the connective-tissue type of malignant tumour, which in mankind comprises only from 6 to 15 per cent. of all malignant growths, in animals is at least as frequent as the epithelial form, and some pathologists consider that it is more frequent.

Johne found, as the result of post-mortem examination, that sarcomata comprised 47 per cent. of the total tumours met with in horses, 37 per cent. in cattle, and 28 per cent. in dogs; while the corresponding figures for malignant epithelial tumours were, 22 per cent. for horses, 8 per cent. for cattle, and 52 per cent. for dogs.

With regard to the site incidence of malignant tumours in animals, as compared with human beings, the most striking fact is the comparative rarity of these tumours in many localities, where they are of very frequent occurrence in humanity—*e.g.*, the stomach, liver, uterus, intestine, tongue, and mouth.

The comparative rarity of gastro-intestinal types of cancer in animals is very marked; thus, 1,312 cases of cancer in common domestic animals (horse, ox, dog, sheep, cat, and pig), as tabulated by Sticker [1] (1,170 cases), Bashford, McFadyean, Cadiot and Roger, comprise only twenty instances of malignant disease of the stomach, or about 1·5 per cent.; whereas, for human beings, the corresponding figure is about 17 per cent.: in like manner, the same series comprises only 42 cases of malignant disease of the liver, or 3·2 per cent.; whereas, in mankind, the corresponding percentage is about 13·5. The only form of gastro-intestinal malignant disease at all common in these animals, is that which affects the anus, of which there were 97 examples, or 7·4 per cent., a figure greatly in excess of the corresponding human ratio, for I have found that only 0·37 per cent. of human cancers are thus situated. This anal form of malignant disease is of more frequent occurrence in the dog, than in any other of the animals mentioned; for, of 738 canine cancers, Sticker found that 89, or 12 per cent., were thus located.

The rarity of lingual cancer in these animals may be judged from the fact, that only four examples are comprised in the 1,312 cases, or 0·3 per cent.; to these may be added 16 cases of cancer in the mouth (chiefly of the gums). Thus, we get 20 cases of cancer of the tongue and mouth, or 1·5 per cent., the corresponding figure for humanity being 3·5 per cent.

Only 26 cases of uterine malignant disease—all from Sticker's list—are comprised in these 1,312 cases, or about 2 per cent. of the total, the corresponding figure for humanity being about 12 per cent.

By way of contrast with the foregoing, mammary cancers are of

[1] *Arch. f. klin. Chir.*, 1902, Bd. lxv., pp. 616, 1023.

commoner occurrence in these animals than in mankind; for, of the 1,312 animal tumours, no less than 360 were thus located, or 27·4 per cent., the corresponding figure for humanity being only 8 per cent. This frequency of mammary cancer in these animals, is due to the great preponderance of this form in dogs, as shown by Sticker's list, which comprises 341 cases of canine mammary cancer in a total of 738 malignant tumours in dogs, or 46 per cent.

Cutaneous manifestations of the disease comprise 16 per cent. of the animal series, this localization being of very frequent occurrence in dogs; whereas, in humanity, skin cancers comprise only about 2·5 per cent. of the total cases.

According to Johne, most sarcomata in animals originate from the bones.

It will be gathered from the foregoing, that the usual seats of traumata and mechanical injuries, rarely coincide with the site incidence of malignant tumours in animals.

With regard to the sex incidence of the disease in animals, there is a dearth of really satisfactory data; but, available indications point to the conclusion that there is no such great diversity between the sexes in this respect, as is the case with humanity; and from this it may be inferred, that the greater proclivity of the human female is due rather to circumstances connected with her special sheltered environment, than to any peculiarity directly connected with sex. It accords with this, that malignant tumours are of common occurrence in castrated domestic animals of both sexes.

It has been suggested that the immunity of animals from uterine tumours—malignant or otherwise—as compared with humanity, may in some way be due to the absence of menopause, in which they differ from human females.

In humanity, as I shall subsequently have occasion to show, the characteristic feature of the age incidence of cancer, is not—as is generally believed—its increase with advance of years; but, rather, its disproportionate augmentation in the post-meridian periods of life—the liability to the malady waxing as the developmental and reproductive activities wane.

In the animal world, the age incidence of cancer is governed by a similar law, tumours of this kind being very rare in early life, commonest in post-meridian ages, and less frequent in advanced age, as Sticker's data show; thus, of 134 dogs affected with malignant tumours, he found that only one was young, 107 were middle-aged, and 26 were extremely old etc.[1]

Very few instances of congenital malignant tumours in animals are known to me, but Penberthy[2] has met with sarcoma of the chest wall in a newly born foal; and Crisp has seen a large encephaloid tumour on the chest of a lamb.

[1] Of 70 dogs with malignant epithelial tumours, the ages were as follows:—2 to 3 years in 14·3 per cent.; 5 to 6 years in 25 per cent.; 7 to 8 years in 28 per cent.; 9 to 10 years in 20 per cent.; 11 to 15 years in 11·4 per cent. Of 90 horses similarly affected, the age percentages were as follows:—under 4 years old 2·2; 5 to 6 years 4·2; 7 to 8 years 10; 9 to 10 years 15·5; 11 to 12 years 9; 13 to 14 years 11; 15 to 16 years 17·7; 17 to 18 years 12·2; 19 to 20 years 14·4; 23 to 25 years 5·3.

[2] *Journ. Comp. Path.*, etc., 1902, vol. xv., p. 271.

Examples of tumours, malignant and otherwise, have now been demonstrated in all classes of vertebrata; and—although at the present time the pathology of the invertebrata is practically *terra incognita*—it seems probable that in the future similar tumours will be shown to occur in this division also; indeed, a beginning has already been made, for J. W. Williams [1] has described an instance of a pediculated tumour, comprising muscular and glandular elements, in a fresh-water mussel (*Anodonta cygnea*), and similar tumours have been noted by Collinge.[2] Ryder,[3] in an oyster, has also met with a large tumour; and, as is now generally recognized, the formation of pearls is due to a formative process excited by the presence of some foreign body, often a parasite. Invertebrate animals are also very prone to pseudo-plasms, caused by parasitic sporozoa etc.

The very frequent occurrence of malignant tumours in castrated animals of both sexes shows, that ablation of the essential sex glands has no deterrent power whatever on the onset of this malady, but there are rather indications that these mutilations favour its development; thus, nearly 50 per cent. of the horses affected with cancer in Sticker's list, had been castrated.

In the animal world, even more than in mankind, malignant tumours are apt to be confounded with various pseudo-plasms of "chronic inflammatory," tuberculous, microbic, aspergillary, or of unknown infective origin; and, mistakes of this kind are all the more prevalent, because the comparative pathology of animals has hitherto been but little studied. As an example of this, reference may be made to Wehr's [4] experiments as to the transmissibility of "cancer" from dog to dog, which attracted so much attention a few years ago; the so-called "cancer" in this case being nothing but a previously unrecognized kind of venereal pseudoplasm of unknown ætiology, but certainly not cancerous.

In all probability the present hasty identification of "Jensen's tumour"—which is transmissible from mouse to mouse—with cancer, is destined to furnish another memorable example of the same kind of mistake.

According to Rayer [5] and Leblanc, among the older comparative pathologists, carnivorous animals are more prone to malignant tumours than herbivorous ones; whereas, with regard to tubercle, the relative liability is just the converse. In support of this contention Rayer found that cancer was common, and tubercle rare, among birds of prey; while, among non-carnivorous birds, tubercle was the prevalent malady, and cancer was unusual. In support of this observation, it may be mentioned that Rayer's contemporary, E. Rousseau, found that eagles and vultures, confined in the Jardin des Plantes at Paris, not infrequently succumbed with cancer.

Among those who have lately investigated this subject, Johne, Woods Hutchinson, Schutz, Pick and Poll, support Rayer's view.

1 *Journ. of Anat.*, 1890, vol. xxiv., p. 307.
2 *Ibid.*, 1891, vol. xxv., p. 154.
3 Proc. Acad. Nat. Sci., Philadelphia, U.S., 1887.
4 *Arch. f. klin. Chir.*, 1889, Bd. xxxix., S. 226.
5 *Arch. de méd. comparée*, 1843.

In this connexion, it is significant that among our common domestic animals, malignant tumours are of much more frequent occurrence in dogs, than in any others ; thus, of 1,312 cases of malignant tumours in domestic animals tabulated by Sticker etc., no less than 810 were in dogs. Cats are also very liable to cancerous tumours.

In the animal world tubercle is a common disease, especially with our domesticated bovines and birds.

All of these facts, as well as others to which I have already referred, indicate the important part played by the conditions of existence in determining the incidence of cancer ; and, among these conditions, nutrition is one of the most important. In my opinion, Dr. Bashford showed extraordinary lack of understanding of biological principles and scientific insight, when he wrote :[1] "The great diversity of food, habit, and conditions of life generally in animals in which cancer occurs, shows that such external agencies have no causative influence."

With regard to non-malignant tumours, it is noticeable that exostoses and osteomata are very common in all classes of vertebrata, even in reptiles and fishes. Papillomata are also of frequent occurrence in animals. Adenomata are comparatively rare, except in the mamma of dogs. Fibrous and fatty tumours are also extremely rare in animals, wild or domesticated. When we recollect that most of our domestic animals have been bred for thousands of years, with special reference to fattening, this rarity of fatty tumours is all the more remarkable.

## Monkey.

Great interest attaches to the maladies of monkeys, because it is among the highest members of this order that we find the nearest approach in organization to mankind.

Notwithstanding the immense number of these creatures constantly under observation in the zoological collections of Europe, it is a curious fact that only about half a dozen examples of tumours have hitherto been reported, and their comparative immunity from this kind of malady seems to be a reality.

Thus, some time ago, Bland-Sutton[2] examined the bodies of 110 of these animals which had died in the London Zoo, but not a single example of any tumour did he find. Subsequently, H. J. Campbell[3] made thirty-eight similar post-mortem inspections, with the like negative result.

Leblanc,[4] however, long ago reported that he had met with instances of malignant tumours in monkeys, and I expect that they do occasionally occur ; but I can cite only two modern instances.

The first of these is due to Goodhart,[5] who found "cancer" of the pituitary body in an Anubis baboon, from the London Zoo, where the animal had long been a familiar denizen. The tumour—a large, ragged-

[1] Second Annual Report Imperial Cancer Research Fund, 1904.
[2] *Lancet*, 1883, vol. ii., p. 276.
[3] Guy's Hospital Reports, 1891, vol. xlviii., p. 19.
[4] *Clin. Vét.*, August, 1843, p. 343.
[5] Transactions of the Pathological Society, London, 1883, vol. xxxvi., p. 36.

looking object—occupied the pituitary fossa, which it had eroded, and some of the adjacent structures were infiltrated. Histologically it comprised "large epithelial-like cells arranged in some sort of an alveolar manner." There were no secondary deposits. This tumour, together with the brain and skull, are preserved in the museum of the Royal College of Surgeons.

The second instance was met with in a bonnet monkey, only eight months old, by Bland-Sutton,[1] the tumour being an intra-ocular glioma, consisting chiefly of small round cells.

Here also mention may be made of a curious atypical epithelial growth of the cervix uteri of a monkey by Woods Hutchinson,[2] who was in doubt whether it was an adenoma or a carcinoma.

In this connexion reference may be made to the attempts of Shattock and Ballance, Metchnikoff, and others, to transmit human cancer experimentally to monkeys, all of which experiments failed.

Thus, monkeys, like human savages, seem to have very little proclivity to cancer.

Here it may be remarked that the alimentary propensities of these animals are predominantly frugivorous, but a good many of them are not averse to animal food when they can get it. Some kinds are insectivorous, and others feed upon almost anything they can get. As with mankind, many species have a singular liking for birds and their eggs, as alimentary dainties.

With regard to non-malignant tumours, the available data are exceptionally meagre.

Bland-Sutton has met with an instance of leio-myomatous thickening in the uterus of a baboon, which had some resemblance to myoma; and the same observer has also seen a fatty tumour-like mass in the vicinity of each testis of a monkey with hermaphroditic malformation.

According to Otto, exostosis is not uncommon at the tip of the tail of long-tailed monkeys; and, in the museum of the Royal College of Surgeons of Ireland the hand of a monkey is preserved, showing a spongy exostosis of the first phalanx of the little finger.

Monkeys are also subject to hydatid cysts.

These few examples practically exhaust our present knowledge of non-malignant tumours in monkeys.

It is an ancient belief that monkeys in captivity are very prone to tubercle; and, some years ago, a mild sensation was experienced when Bland-Sutton [3] flatly contradicted this cherished conception. In justification of his contention, he appealed to the record of 110 post-mortem inspections of monkeys, which had died in the London Zoo, and comprised only three instances of tubercle. He found, however, that these animals had experienced very heavy mortality from diseases of the lungs—the list comprising 22 examples of bronchitis, 11 of pneumonia, etc.

Some years later H. J. Campbell,[4] as the result of similar work in the same field, arrived at exactly the opposite conclusion, having found that

[1] *Journ. of Anat. and Physiol.*, 1885, vol. xix., p. 449.
[2] "Human and Comparative Pathology," 1901, p. 258.
[3] *Lancet*, 1883, vol. ii., p. 276. [4] *Op. cit.*

tuberculous disease was very frequent in these monkeys. Thus, no less than 20 of the 38 bodies he examined, presented well-marked tuberculous lesions. In addition to these, there were also many cases of bronchopneumonia.

It is evident that these discrepancies depend mainly upon diversity as to the criterion of tubercle. Viewing the matter in this light, we shall probably be right in maintaining the validity of the old belief.

In support of this, reference may be made to the observations of Dr. A. J. Harrison,[1] who has long been connected with the management of the fine collection of animals at the Clifton Zoo. He says : " Monkeys are very liable to chest affections, and there can be no question that we have lost a great many from tuberculous disease of the lungs. They seem very prone to pleurisy, and adhesions are frequently found with and without tuberculous masses in the lungs ; but actual cavities do not seem to be frequent. Monkeys seem to be particularly prone to tubercle."

It accords with the foregoing, that Lydia Rabinowitsch [2] has lately found many examples of tubercle among the monkeys that died in the Berlin Zoo ; and, of 36 cases in which these lesions were specially examined *ad hoc*, in nearly three-fourths the type of tubercle was human, examples of bovine, avian, and mixed types being only occasionally met with.

It has likewise been proved that monkeys are very susceptible to the experimental inoculation of both the human and bovine forms of tubercle, as the experiences of Dieulafoy, Krishaber, Dungern, and others testify.

Of like import is the common occurrence of specimens of simian tuberculous disease in museums, such as that of the Royal College of Surgeons of Ireland, which have good collections illustrative of the pathology of these animals.

According to Woods Hutchinson,[3] monkeys in their native forests are but little prone to tubercle ; but, in captivity, it is difficult to procure specimens free from the disease. Thus, of 45 monkeys that died in captivity at the London Zoo (1898-1899), 17 died of tubercle, or 38 per cent. Food habits have much to do with tubercle mortality ; for, of Hutchinson's animals, 35 were vegetarian Catarrhines, and it was among these that all the 17 deaths occurred ; whereas, not one of the ten deaths among the Platyrrhine monkeys, who had taken a fair amount of animal food, was due to tubercle.

### Dog.

Of all domesticated animals, dogs are by far the most prone to malignant tumours ; thus, of 60,471 canine patients at the Berlin thierärtzlichen Hochschüle (1886-1894), Fröhner [4] found that 2,871 had some form of tumour, of which 1,154 were cancerous, or 1·9 per cent. of the total ; of 1,306 dogs examined, Sticker [5] reports that 72, or 5·5 per cent., had cancer ; while, according to Semmer,[6] of 3,525 dogs examined at his clinic, 8 per cent. were cancerous.

1 *Bristol Med. Chir. Journ.*, 1894, vol. xii., p. 285.
2 *Deutsche med. Woch.*, May 31, 1906, S. 866.
3 " Human and Comparative Pathology," 1901.
4 *Monats. f. prakt. Thierheilkunde*, 1895, Bd. vi.
5 *Arch. f. klin. Chir.*, 1902, Bd. lxv., p. 616 *et seq.*
6 " Lehrb. d. allgem. Chir. u. Operationslehre " (Möller), 1893.

These figures indicate that cancer is even more prevalent among dogs, than among human beings.

All the chief types and varieties of cancer met with in mankind, also prevail among dogs. Epithelial and sarcomatous forms are common. Melanotic and myxomatous varieties also occur; and a form of disease, "presenting the histological features of rodent ulcer," has also been seen. Malignant tumours containing heterotopic structures—cartilage, bone etc.—are common. Leukæmia also occurs.

According to Johne, of 93 tumours found post-mortem in dogs, 28 per cent. were sarcomatous.

Most of the affected animals are domestic pets; but, as previously mentioned, Brooks has met with sarcoma of the ovary, in a wild racoon-dog, that had been kept for two years in captivity. Three-quarters of these animals were from five to ten years old; and Fröhner says he has never seen a malignant tumour in a dog under two years old.

Sticker's analysis of 738 cases of canine cancer, shows that the commonest seats of the disease are the mamma (45 per cent.), skin (21 per cent.), anus (21 per cent.), liver (3 per cent.); and, less frequently, the kidney, testis, penis, prostate, eye, bladder, vagina, lung, thyroid, ovary etc. Very remarkable is the great rarity of gastric cancer, of which there was only one instance; the intestine provided not a single example; and in only two cases was the uterus affected.

Of the malignant mammary tumours of female dogs, those of the epithelial type predominate; thus, of 18 tumours of this kind, histologically examined by Cadiot and Roger,[1] 11 were glandular epitheliomata, and 7 were sarcomata. Other interesting series of malignant mammary tumours have been reported by Ortschild,[2] Cornil and Petit,[3] and MacFadyean.[4]

The usual type of malignant epithelial tumour of the dog's mamma, resembles that which is so frequent in the breast of the human female—the acinous variety predominating; but tubular forms are also met with, which are often associated with cysts and intra-cystic papilliferous growths, as in humanity. Acute and chronic varieties of the disease also occur, and the colloid form has also been reported (Gibbes). Melanotic mammary cancer has been noted (Crisp etc.). In short, every variety of mammary cancer that has been discriminated in mankind, may be matched in the dog. The hindermost glands of the series are most prone to be affected. Male dogs have relatively greater proclivity to mammary cancer, than male humanity.

In dogs, these malignant mammary tumours are much more frequently associated with gross heterotopia—cartilaginous, osseous, calcareous formations etc.—than are the corresponding tumours of humanity. G. Petit[5] has lately published a good study of the pathology of these canine "mixed tumours."

With regard to mammary sarcomata, these are relatively of more

[1] "Bouchard's Traité de Path. Gén.," 1895, t. i.
[2] *Johns Hopkins Hosp. Bull.*, 1905, vol. xvi., p. 185.
[3] *Bull. et Mém. Soc. Anat. de Paris*, 1905, t. lxxx., p. 137.
[4] *Journ. of Comp. Path.*, etc., 1890, vol. iii.
[5] *Bull., etc., de la Soc. Anat. de Paris*, 1906, No. 5, p. 373.

frequent occurrence in canine than in human pathology; and they also are very much more frequently associated with gross heterotopia: Cadiot and Roger found structures of this kind in five out of seven specimens examined. Cystic and adenoid formations are as common as in the corresponding human tumours; and, as in the latter, spindle-celled elements predominate. Alveolar, melanotic, and myxomatous forms of the disease have also been met with.

Of the numerous attempts by Ortschild, Gratia, and Liénaux, to transmit these tumours by implantation to other dogs, all were unsuccessful.

Of non-malignant mammary tumours, adenoma, fibroma, enchondroma, osteoma, papilloma, and cystoma have been reported.

Mammary fibro-adenomata are not uncommon in female dogs, and Ortschild has described an instance of the same malady in a male. These tumours also are fairly often associated with heterotopic elements, such as bone and cartilage, of which Rolleston [1] has studied examples.

An interesting case of villous papilloma was some time ago seen by J. W. Sibley [2]—"A multilocular cystic tumour, with villous intra-cystic growths, from the mamma of a bitch"—and Ortschild has lately met with a similar case.

Enchondromatous and osteoid tumours of the mamma of female dogs are comparatively common, as was long ago shown by Lebert, J. Müller, Virchow, etc., and modern instances of this kind have been studied by Adams, Langlois, Gowing etc.

Several examples of malignant disease of the normally placed and of the ectopic testis in dogs have been recorded; as also of cancer supervening after injuries; thus, in a setter dog, Birchmore saw sarcoma form after a gunshot wound of the jaw.

With regard to the reputed frequency of malignant disease in the anus and its vicinity, which is a special feature of the neoplastic pathology of the dog, it is evident that this matter requires further investigation. It is already known, however, that a benign adenomatous tumour not uncommonly develops in this vicinity—probably from the circum-anal scent-glands—the exact nature of which is still *sub judice*. These tumours are circumscribed, lobulated, and easily shelled out; histologically they consist of solid cylinders of epithelial cells—which are sometimes pigmented—regularly arranged in delicate vascular connective tissue. Tumours of this kind have been known to recur after removal (MacFadyean,[3] Wallace [4] etc.); and it is believed that one form of malignant disease of the anus arises from this source.

Anal cancers of the epidermoidal type also occur.

G. Petit[5] has given an interesting account of several cases of "branchiogenic" cancer of the neck in dogs.

Among the non-malignant tumours met with in these animals, reference may be made to fibromyomata of the uterus, of which instances

[1] Transactions of the Pathological Society, London, 1897, vol. xlviii., p. 324.
[2] *Ibid.*, 1858, vol. xi., p. 460.
[3] *Practitioner*, April, 1899, p. 460.
[4] Transactions of the Pathological Society, London, 1896, vol. xxxviii., p. 659.
[5] *Rec. de Méd. Vét.*, 1902, p. 673.

have been reported by Keiffer,[1] Wagner,[2] E. H. Williams and Hobday ;[3] and, in the vagina, similar tumours have been found by Aulton and Hobday,[4] Leisering etc.

Cases of ovarian cystomata have also been recorded in veterinary publications ; and a tumour of this kind has been known to attain a weight of 15 pounds.

Examples of adenoma of the liver (Schweizer and others), of the kidney (Jung), and polypoid adenoma of the trachea (Bidwell), are also on record.

Cavernous angioma of the liver has been seen by Petit and Virchow.

A big fibrous tumour, which contained osteoid deposits, from the popliteal space of a large dog, is comprised in the pathological collection of the Hunterian Museum (No. 800).

A large retro-peritoneal lipoma has been seen by A. J. Williams[5] and by L. Hudson.[6] Ortschild[7] met with a similar tumour in the paravaginal region ; and also in the left pectoral region—the latter animal being also affected with a malignant " mixed " tumour of the mamma.

A bony growth, connected with the cervical vertebræ, has been described by Viborg.

Branchial cysts have been met with by G. Petit and others, while Cathelin has seen a cyst connected with the small intestine, and Ortschild cystic hygroma of the shoulder.

Solid and cystic goitrous tumours also occur, of which many cases have been recorded (Morell Mackenzie, Faris etc.).

Papillary cutaneous excrescences are of common occurrence ; warts also occur in the mouth and on the foot-pads of dogs.

In a subcutaneous fibroid swelling, Lefas found included epidermoidal structures ; and Petit[8] has seen a branchial dermoid cyst of the neck.

Several instances of dermoid hairy patch on the ocular conjunctiva have also been described (Dobson, Taylor etc.).

Besides the contagious venereal growths previously referred to, dogs are also prone to contagious papillomata of the mouth, which are transmissible by artificial means, and resemble the " sublingual tumour " of human nurslings as described by Riga and Fede.

Dogs are comparatively speaking but little prone to tubercle ; yet tumour-like swellings due to this cause, to pseudo-tubercle, actinomycosis, streptothrix and other mycotic infections are met with. Pick and Poll have found *quasi*-malignant gastric tumours, due to the presence of *Spiroptera sanguinolata*, a small parasitic nematoid worm. Hydatids also occur. Examples of quasi-malignant tumours, caused by the injection of cultures of various microbes, are elsewhere referred to.[9]

In further illustration of the subject of canine malignant tumours, the following additional references may be useful :

[1] *Bull. de la Soc. Belge de Gyn. et d'Obstét.*, 1900, t. x., p. 231.
[2] *Cent. Bl. f. allg. Path.*, etc., 1905, vol. xvi., Heft 4.
[3] *Journ. of Comp. Path.*,' 1902, vol. xv., p. 267.
[4] *Veterinary Journal*, May, 1905, p. 255.
[5] *Veterinarian*, June, 1897, p. 301.
[6] Transactions of the Pathological Society, London, 1890, vol. xli., p. 401.
[7] *Op. cit.* [8] *Rec. de Méd. Vét.*, 1905, No. 4, p. 60.
[9] Chapter X.

Six cases of cancer of the breast, with inoculation experiments, by Gratia and Liénaux ;[1] cancer of mamma of a bitch, by Monsarrat ;[2] three cases of cancer of the axillary sweat-glands, by Creighton ;[3] melanotic cancer of the mamma of a terrier bitch, with dissemination in the lungs, by Crisp ;[4] cystic chondro-sarcoma of the mamma of a bitch, by Rolleston ;[5] cysto-sarcoma proliferans of the mamma of a greyhound, with secondary formations in the liver and spleen, and cystic disease of the ovaries, by Bertolet ;[6] chondro-osteo-sarcoma of the mamma of a bitch, by Virchow ;[7] cases of retro-peritoneal and peri-tracheal sarcoma in young dogs, by Spencer ;[8] cases of cystic myxo-sarcoma of the neck, by Creighton ;[9] " un cas de chondro-sarcoma intestinal generalisé au poumon," by Petit ;[10] cancer of prostate, by De Rouville ;[11] columnar epithelioma of lung, by Silcock ;[12] cystic sarcoma of the testis of an Italian greyhound ;[13] melanotic sarcoma of the immediate vicinity of the scrotum in a Welsh terrier, by Leon ;[14] similar disease from the foot of a dog ;[15] " myxo-sarcomatodes medullare " of the vagina, by Kaschewarowa-Rudnewa ;[16] fibro-spindle-celled sarcoma of the intestine, with invasion of the great omentum and mesenteric glands, by Petit ;[17] sarcoma of the palate of an otter-hound, by Lediard ;[18] osteo-sarcoma of the thigh, by G. Petit ;[19] sarcoma of the olfactory lobe, by Marchand and Petit ;[20] cases of Hodgkin's disease, by MacFadyean ;[21] lymphomatous tumours of the spleen, by H. V. Williams [22] etc.

### Cat.

Judging by the comparative paucity of published cases, cats are much less prone to malignant tumours than dogs ; but, according to the records of the Veterinary Pathological Institute of Berlin, this is not so ; for of 34 cats there examined, 2, or 5·9 per cent., were thus affected. The usual primary seats of the disease in cats are the mamma and skin ; other parts liable being the lung, pleura, liver, tongue, ovary, penis, eye, anus, lip etc. Most of the malignant forms of epithelial and connective-tissue tumours, including the melanotic, have been reported in cats. Carcinomatous tumours of the mamma of the acinous and tubular types are met

[1] " Ann. de Méd. Vét.," Bruxelles, 1894.
[2] *Liverpool Med. Chir. Journ.*, 1900, vol. xx., p. 132.
[3] Transactions of the Med.-Chir. Society, London, 1882, vol. lxv., p. 53.
[4] Transactions of the Pathological Society, London, 1848, vol. ii., p. 346.
[5] *Ibid.*, London, 1897, vol. xlviii., p. 324.
[6] *Philadelphia Medical Times*, U.S., 1872-1873, vol. iii., p. 315.
[7] " Würzburger Verhandl.," Bd. i., S. 137.
[8] Transactions of the Pathological Society, London, 1891, vol. xlii., p. 472.
[9] *Journal of Anatomy*, vol. xiv., p. 292.
[10] *Bull. Soc. de Méd. Vét.*, Paris, 1905, vol. lix., p. 283.
[11] *Bull. Soc. Anat.*, Paris, July, 1896.
[12] Transactions of the Pathological Society, London, 1886, vol. xxxvii., p. 570.
[13] " Catalogue Hunterian Museum. Path. Suppl.," p. 71 (No. 4,235).
[14] *British Medical Journal*, 1899, vol. ii., p. 1046.
[15] " Catalogue Hunterian Museum," Path. Series, No. 469A.
[16] *Arch. f. path. Anat.*, 1872, Bd. liv., S. 73.
[17] *Bull. Soc. Anat.*, Paris, 1899, p. 487.
[18] Transactions of the Pathological Society, London, 1888, vol. xxxix., p. 458.
[19] *Rec. de Méd. Vét.*, February, 1906, p. 81.
[20] *Bull. Soc. Anat.*, Paris, 1906, No. 5, p. 397.
[21] *Journ. of Comp. Path.*, etc., 1903, vol. xvi., p. 379.
[22] *Journal of Medical Research*, 1902, vol. vii., p. 408.

with; among those who have recently studied specimens of this kind are Petit,[1] Leiden,[2] Spencer,[3] and Eva Field.[4]

The last named has also described an example of cystic round-celled sarcoma of the subcutaneous tissue below the ear; and Breton and Petit[5] a case of intra-ocular sarcoma of the globe of the eye; while Stroud[6] has met with sarcoma of the ovaries and pelvis.

There is a specimen of cancellous exostosis of the lower jaw in the Hunterian Museum;[7] and a similar formation connected with the upper part of the femur is in Guy's Hospital Museum. The Hunterian Museum also exhibits the omentum of a cat studded with small, stalked, fibro-fatty outgrowths; and angiomata of the liver has also been noticed.

An example of sublingual ranula has been seen by Ridler and Hobday,[8] and the same authors have also reported a case of nasal polypus.

Like other carnivorous animals, cats are but little prone to tubercle.

## Horse.

Malignant tumours in horses are decidedly rare, for, according to Sticker, of 215,037 of these animals under treatment at the Berlin "Hochschule" Veterinary Clinic, only 103 were thus affected, or 0·046 per cent. However, many cases are on record in the veterinary journals; and of Sticker's 1,170 tabulated cases, 318 were in horses.

The commonest primary seats of the disease are:—the antrum and the adjacent naso-oral cavities[9] (16 per cent.), the penis (16 per cent.), kidney (9 per cent.), skin (7 per cent.), lung and pleura (5·6 per cent.), bladder[10] (4·4 per cent.), testis (4 per cent.), eye (4·4 per cent.); and in lesser degrees of frequency, the vulva, gum, stomach, anus, mamma,[11] uterus, vagina, intestine, ovary, larynx, tail[12] etc.

Not a single example of malignant disease of the tongue is comprised in the 356 cases in horses, tabulated by Sticker, MacFadyean, Bashford, Cadiot and Roger; and it is noticeable that gastric, intestinal, and uterine malignant tumours, are exceedingly rare in these animals.

The melanotic form of tumour disease is of common occurrence in horses, especially in those of white, grey, roan, and dun tints; but even the black varieties are not exempt. Its commonest seats are the anus, root of the tail, external genitals, skin etc. Most formations of this kind are of a chronic nature, and comparatively benign—these are described by Cornil and Trasbot[13] as fibromata; but occasionally they

[1] *Bull., etc., Soc. Anat.*, Paris, 1905, t. lxxx., p. 137.
[2] *Zeits. f. klin. Med.*, 1904, vol. lii., p. 409.
[3] Transactions of the Pathological Society, London, 1890, vol. xli., p. 400.
[4] *Journal of American Medical Association*, December 29, 1904, p. 983.
[5] *Rec. de Méd. Vét.*, Paris, 1902, t. ix., p. 38.
[6] *Veterinary Journal*, June, 1902, p. 317.
[7] "Path. Catalogue," vol. iii., p. 12.
[8] *Veterinary Journal*, June, 1905, p. 333.
[9] For a case, the cheek being the part affected, *vide Journ. of Comp. Path.*, 1903, vol. xvi., p. 161.
[10] Case by MacFadyean, *Journ. of Comp. Path.*, 1902, vol. xv., p. 148.
[11] For a case, *vide Journ. of Comp. Path.*, 1903, vol. xvi., p. 161.
[12] Case by MacFadyean, *Journ. of Comp. Path.*, 1902, vol. xv., p. 148.
[13] "De la Mélanose," 1868.

manifest all the properties of malignancy, with widespread dissemination, and are then generally described as being of sarcomatous structure, spindle cells predominating. Melanotic tumours sometimes attain great size, weighing as much as from 20 to 60 pounds; and some remarkable instances of their heredity are cited by Virchow.[1] Lebert[2] mentions a case in which a black tumour, that had long existed under the root of the tail at length became generalized, thousands of small tumours forming in the lungs, liver, peritoneum, pericardium, spleen, and in many other parts. The Royal College of Surgeons Museum in London contains two interesting specimens of this malady prepared by Hunter:

1. No. 290, Pathological Series: "A section of the tail of a horse, and of a large, lobulated, soft, pale brown and black tumour, embedded deeply in its substance, and projecting in lobes and lobules on its surface."

2. No. 291, Pathological Series: "Melanotic tumour removed from the neck of a horse. It is black throughout, firm, lobulated, and loosely encapsulated (10 by 5 inches). It was removed by Hunter from the inner side of the jugular vein, which passed over it."

A good example of the malignant form of melanosis, with widespread dissemination, has been described by Hutchinson.[3] Bloodgood[4] has met with the same disease in the liver, and G. Petit[5] within the spinal canal.

A specimen of intra-ocular melanoma, which filled the whole globe, and had involved also the orbit, is contained in the Hunterian Museum (No. 2,259, Pathological Series).

Epidermoidal cancer of the membrana nictitans, with dissemination, has been described by MacFadyean;[6] and instances of epidermoidal cancer of the ocular conjunctiva by Petit and Coquot,[7] and by Taylor.[8]

Malignant tumours are of specially frequent occurrence in gelded animals; thus, of seven examples of epidermoidal cancer of the penis in MacFadyean's list, all were from geldings.

Instances of epithelioma of the penis have been studied by Patteson,[9] and Webber,[10] of the vulva by Petit,[11] and of the vagina by Bashford.[12]

Of 128 tumours found post-mortem in the horse, Johne found that 60, or 47 per cent., were sarcomatous.

An example of "alveolar sarcoma" of the upper jaw has been published by Pike;[13] and veterinary museums generally contain specimens of "spina ventosa" of this locality, most of which are due to sarcomatous tumours. Malignant epithelial tumours, mostly of the epidermoidal type, also arise from the antrum.

[1] "Path. des Tumeurs," 1869, t. ii., p. 236.
[2] "Traité des Mal. Cancéreuses," p. 159.
[3] *Archives of Surgery*, 1890, vol. iv., p. 48.
[4] *Johns Hopkins Hospital Bull.*, June, 1905, p. 239.
[5] *Bull. et mém. Soc. Anat.*, Paris, 1905, No. 5, p. 382.
[6] *Journ. of Comp. Path.*, 1904, vol. xvii., p. 352.
[7] *Rec. de Méd. Vét.*, 1905, t. lxxxii., No. 1, p. 10, with excellent clinical and histological figures.
[8] Royal London Ophthalmic Hospital Reports, 1876, vol. ix., p. 74.
[9] *Illustrated Medical News*, December, 1888, p. 220.
[10] *British Medical Journal*, 1899, vol. ii., p. 882.
[11] *Rec. de Méd. Vét.*, Paris, 1902, vol. ix., p. 118.
[12] Proceedings of the Royal Society, London, 1904, vol. lxxiii.
[13] *British Medical Journal*, 1896, vol. i., p. 989.

Sarcomatous tumours of the lower jaw have been reported by Lediard[1] and Waldmann;[2] while many examples of "spina ventosa" of this bone are to be found in veterinary museums.

Actinomycetic tumours of the naso-oral region, which are of common occurrence in horses, require to be discriminated from malignant tumours of this vicinity, which they often closely simulate.

Sarcomatous tumours growing from the ribs, ulna, etc., have also been met with.

Several cases of leukæmia, and of intra-thoracic lymphadenoid disease have been recorded (Petit, Weil etc.).

Malignant disease of the retained testis has been seen by Axe[3] and others; while several cases of ossifying chondro-sarcoma, and of carcinoma, of this organ are on record (Gamgee etc.).

Examples of intra-ocular and orbital sarcoma are referred to by Axe; and there is a specimen of this kind in Guy's Hospital Museum.

Several specimens of mammary carcinoma in the mare have been met with (MacFadyean, Cadiot and Roger etc.); and a large cystic fibro-adenomatous tumour of this part in a mare, which comprised ossifying and chondromatous structures, and was of "a quasi-carcinomatous nature in some parts," has been described by Scott.[4]

Eight instances of cancer of the uterus, 7 of the vagina, 4 of the ovary, and 8 of the stomach, are included among Sticker's 318 malignant horse tumours; and Bland-Sutton has seen 2 cases of uterine sarcoma.

An example of ulcerated cancer of the skin behind the ear, which was ascribed to the irritation of a papillary excrescence by the bridle, has been met with by Birchmore;[5] and Woods Hutchinson has seen sarcoma of the lip of a horse.

I have previously referred to Penberthy's case of congenital sarcoma of a foal.

Judging by the numerous specimens of exostoses and osteomata contained in the chief museums, horses must be very prone to these formations. I have references of growths of this kind connected with the spine, pelvic bones, inferior maxilla, ribs, sternum, scapula, humerus, cannon bone, gluteal aponeurosis, palate, nasal septum, etc.

Ivory exostoses of the skull bones, like those met with in human pathology, also occur; and a tumour of this kind, as big as a man's fist, has been known to have been shed spontaneously from the nostril of a horse. Loose bony and cartilaginous tumours have also been found in the knee-joint.

Many instances of exostoses due to ossification of the tendons of muscles, have also been met with.[6]

Some remarkable instances of odontomata and dentigerous so-called "cranial dermoids" have been described by Broca,[7] chiefly from speci-

[1] Transactions of the Pathological Society, London, 1884, vol. xxxv., p. 468.
[2] *Zeits. f. Thier-med.*, 1899, Bd. iii., S. 199.
[3] *Veterinarian*, vol. xxv., p. 262.
[4] *Veterinarian*, July, 1895, p. 462.
[5] *New York Medical Journal*, 1883, vol. xxxviii., p. 659.
[6] For references to cases, *vide* Barrier, *Rec. de Méd. Vét.*, 1905, t. lxxxii., No. 6, p. 115.
[7] "Traité des Tumeurs," 1869, t. ii., chap. x.

mens in the celebrated Alfort and other veterinary museums. Aberrant teeth in horses have also been noted in the palate bone, and more rarely in the petrous bone; and probably some of these odontomata arise from redundant, aberrant tooth germs.[1]

A peculiar kind of symmetrical hyperostosis of the maxillary bones of West African horses and mules—recalling the affection known as "goundrou," which occurs among the negroes of the Ivory Coast—has been studied by Zieman[2]; and Ridewood[3] exhibited not long ago at the Linnean Society a specimen of a similar condition, bu the regarded the symmetrical bony bosses as indications of a pair of rudimentary horns!

Horses are liable to fibrous and papillary growths; while sebaceous cysts and horny excrescences have also been noted.

Virchow,[4] R. W. Smith,[5] A. Thomson,[6] and De Boinville,[7] have reported instances of multiple fibro-neuromata in horses and other domesticated animals.

In the body of an old mare, sent to the Clifton Zoo to be slaughtered as food for the carnivora, Harrison[8] found an enormous fibro-myomatous tumour of the uterus; and Virchow had previously called attention to tumours of this kind, in the uterus and vagina of horses and other animals.

A large fibro-myomatous tumour of the duodenum of a mare, which had caused fatal intestinal obstruction, has been described by Cadéac[9]—extensive areas of the tumour being in a state of fatty degeneration.

A good many instances of polypoid adenomatous tumours of the intestine projecting within the gut, have also been found. An ossified tumour of this kind of the cæcum, has been reported by G. Petit,[10] who has also met with a similar growth in the rectum, which was undergoing calcification;[11] and peri-anal adenomatous tumours also occur.

Several instances of pedunculated so-called fatty tumours connected with the small intestine, which had caused fatal intestinal obstruction, have also been recorded in veterinary publications; and these tumours are generally referred to as overgrown appendices epiploicæ; but, in the light of Cadéac's case, some of them may be otherwise derived.

To such sources as the foregoing, many of the foreign bodies—often of considerable size—found free in the peritoneal cavity, may be referred.

Large intra-abdominal fatty tumours have also been met with in horses and other domesticated animals (Fürstenburg). Hobday[12] has seen lipoma in the undescended testis, which specimen is now preserved in the Hunterian Museum; and MacFadyean has seen two examples of subcutaneous lipoma of the fore-leg.

[1] Ridler, "Dentigerous cyst in the vicinity of the ear of a Mare, which contained two odontomatous masses, one of great size," *Journ. of Comp. Path.*, etc., 1902, vol. xv., p. 266; also Hobday, *ibid.*, vol. xii., p. 174.

[2] *Journal of Tropical Medicine*, London, May 1, 1905, p. 135.

[3] Proceedings of the Linnean Society, October, 1904, p. i.

[4] "Path. des Tumeurs," t. iii., p. 496.

[5] "Sydenham Society's Atlas. Illust. Path.," fasc. xi.

[6] "Neuroma and Neuro-fibromatosis." Edinburgh, 1900.

[7] *Veterinary Journal*, March, 1905, p. 130.

[8] *Bristol Med. Chir. Journ.*, 1894, vol. xii., p. 288.

[9] *Rec. de Méd. Vét.*, March 15, 1885.

[10] *Bull. et mém. Soc. Anat.*, Paris, January, 1902.

[11] *Rec. de Méd. Vét.*, 1905, No. 6, p. 122.

[12] Transactions of the Pathological Society, London, 1906.

Ovarian and parovarian cysts are not unknown; and a tumour of this kind has been reported, which weighed as much as 84 pounds.

Ovarian dermoids are also found; and, in a case of this kind by Pollock,[1] in addition to piliferous pigmented skin, the tumour contained cartilaginous and ossifying structures.

Tumours of somewhat similar composition have also often been found in connexion with the testis, especially during castration.[2]

Dermoid cysts, sometimes containing teeth, have been met with in the temporal, petrous, and sphenoid regions; while Leblanc[3] has seen an intra-cranial piliferous dermoid.

Horn-like cutaneous outgrowths often occur in horses.

Spencer[4] has reported a case of polycystic disease of both kidneys, so diffused that hardly any normal renal structure could be seen.

Cysts of the unobliterated urachus have been met with in horses, cows, pigs, etc.

Horses are singularly liable to the formation of large intra-cerebral tumours, in connexion with the choroid plexuses—the so-called "psammoma"; or, by reason of their richness in cholesterine, "cholesteatoma," of which examples have been reported by McCarthy,[5] Saundby,[6] MacFadyean[7] etc.

A unique case of rhabdo-myoma of the subcutaneous shoulder region, has been described by Monod,[8] in which the tumour was attached by a long thin pedicle to the scapula.

Horses, mules, and asses are also subject to goitrous thyroid tumours.

Malignant tumours occur in *mules* and *asses;* but I have found very few cases of this kind on record.

An instance of round and spindle-celled sarcoma of the lower lip of a mule, following injury by the bit, has been reported by Birchmore; and these animals, as well as asses, are liable to melanosis.

In the ass, cases of sarcoma of the colon, testis, and of the lung (chondro-sarcoma) have also been published.

Pseudo-plasms consequent on actinomycosis, aspergillosis, bothryomycosis, and other parasitic affections, are of not uncommon occurrence in horses; and Hutchinson[9] has described an example of intra-ocular hydatid cyst. Tuberculosis occurs, but it is not common. Tumour-like swellings in the walls of the stomach, due to œstrus larva, have also been noted. A tumour-like lesion of the lung, due to blastomycetic infection, has been reported by Frothingham;[10] a mycotic maxillary tumour by Foulerton,[11] and a fibroid tumour-like mass of the spermatic cord, due to bothryomycosis, by Wolstenholme.[12]

[1] Transactions of the Obstetric Society, London, 1890, vol. xxxi.
[2] *Vide Journ. of Comp. Path.*, etc., 1903, vol. xvi., p. 127; *ibid.*, 1905; April, p. 210; and Transactions of the Pathological Society, London, 1906.
[3] *Rec. de Méd. Vét.*, t. viii., p. 342.
[4] Transactions of the Pathological Society, London, 1890, vol. xli., p. 397.
[5] *Univ. Pennsylvania Med. Bull.*, U.S., October, 1904, p. 265.
[6] *British Medical Journal*, 1882, vol. ii., p. 896.
[7] *Journ. of Comp. Path.*, etc., 1902, vol. xv., p. 162.
[8] *Rec. de Méd. Vét.*, June 30, 1902.
[9] Transactions of the Pathological Society, London, 1857, vol. viii., p. 413.
[10] *Journal of Medical Research*, Boston, U.S., 1902, vol. viii., p. 31.
[11] Transactions of the Pathological Society, London, 1900, vol. li., p. 51.
[12] *British Medical Journal*, 1902, vol. i., p. 84.

### Ox.

In bovine animals, according to Sticker, malignant tumours are very uncommon; for of 5,795, only 7 were thus affected.

The same authority states that their commonest seat is the uterus (16 in 74 cases); but I find that the liver[1] and stomach head the lists of most pathologists. Other parts liable to be affected are:—the kidney, bladder, ovary, lung, eye, skin, vulva, penis, vagina, adrenal etc.—all the chief varieties of malignant disease being represented.

In the Chicago stockyards, Jobson and Loeb[2] found that cancer of the ocular conjunctiva was the commonest form; and cancer of the vulva was also met with.

There is a specimen of cancer of the rectum in the Hunterian Museum (No. 1,265, Pathological Series); and also of melanoma of a white cow's udder (No. 469, Pathological Series).

Cadéac[3] has met with melanotic fibroma of the buttock of a cow seven years old, and he refers to other cases of the kind; the Hunterian Museum contains a melanotic tumour, the size of a man's fist, which was removed from near the knee of a young cow; and Bashford[4] has seen cases of melanotic sarcoma of the perineum and thigh of young cows.

Hamburger[5] has described "chondro-fibro-melano-sarcoma" of the pleura and diaphragm of a cow; and Pike[6] "alveolar sarcoma" of the submaxillary region of a young bullock.

Examples of "spina ventosa" of the superior and inferior maxilla, of the metacarpal and pastern bones, etc., are to be found in veterinary museums.

Exostoses and osteomas are as common in bovine animals as in horses; in the Hunterian Museum (No. 3,216, Pathological Series) is a large ivory exostosis from the frontal bone of an ox, which weighs 16 pounds, and measures 8½ inches in diameter. Odontomata also occur.

On examining the body of an apparently healthy cow, Colin[7] found the nerves studded with innumerable tumours (neuro-fibromata), mostly of small size; but, in connexion with the solar plexus, there was a large tumour, which weighed 5 pounds: other cases of this kind are referred to by Virchow.

"Fibroid" tumours of the uterus, vagina, and submucosa of the stomach occur; and in the Hunterian Museum (No. 194, Pathological Series) is an encapsuled bilobed tumour, of fatty appearance, attached by a long pedicle to the intestine of an ox.

Cutaneous horns are sometimes met with; in the Hunterian Museum there is a specimen of a large growth of this kind from the skin of the

[1] For note as to the frequency of "adeno-carcinoma" of the liver in Irish cows, *vide* Trotter (*Journ. of Comp. Path.*, 1904, vol. xvii., p. 127). May not many of these tumours be due to some as yet undiscriminated microbic infection? This is suggested by the undue incidence of the disease in the liver.

[2] *Arch. f. klin. Chir.*, Bd. lxx., 1903, p. 845; also *Medicine*, April, 1900.

[3] *Rec. de Méd. Vét.*, March 15, 1885.

[4] Scientific Report of the Cancer Research Fund, No. 2, 1905.

[5] *Arch. f. path. Anat.*, Bd. cxvii., p. 427.

[6] *British Medical Journal*, 1896, vol. i., p. 989.

[7] *Rec. de Méd. Vét.*, t. viii., p. 947.

forehead of an ox : similar formations have been seen on the neck and elsewhere.

Ebinger[1] has recorded an instance of lipoma, found within the spinal canal of a cow.

Papillary growths of the penis, vagina,[2] gall-bladder,[3] tongue, œsophagus, etc., have been met with.

Mammary adenomata and fibromata are fairly common.

Multiple polypi of the mucosa of the small intestine of a cow have been reported by MacFadyean.[4]

Ovarian cystoma are not very exceptional, often attaining great size; an example of multiple myomata of the uterus has been described by Spreull,[5] in which there were fifteen large tumours—each about the size of a melon—and many small ones.

Cysts of abdominal, renal, intestinal, vaginal, and vesical location have also been reported; and hydatids are common.

Specimens of dermoid cysts containing hairs, teeth, etc., are to be found in the Hunterian and other museums; and Windle[6] has met with a teratoma of the sphenoid in a calf.

In the Hunterian Museum (No. 161, Pathological Series) is a dermoid cyst from the shoulder of a cow with six legs; the cyst contained hairs, fatty, and calcareous matter. An instance of a branchial dermoid cyst of the lower part of the neck by Trotter,[7] is also on record.

Bovine animals are specially prone to tubercle, as well as to the same kinds of pseudo-plasms as horses.

### Pig.

There is a consensus of opinion among veterinarians, which finds some support in the paucity of recorded cases, that malignant tumours are of rare occurrence in swine. Of over 100 malignant tumours examined by MacFadyean, Cadiot, and Roger, there was not a single example from a pig; and Sticker's list of 1,170 similar tumours comprises only 12 from this animal. Gaylord and Zink[8] found 4 malignant tumours among about 2,000 swine, mostly young, slaughtered at Buffalo. Judging by recorded cases, the kidney, skin, and liver are the commonest seats of initial manifestation. Other localities noted are intra-abdominal, lymph-glands, submaxillary gland, parotid, testis, penis, maxillary bones, vertebræ etc.

Hamburger[9] has made detailed study of a case of kidney sarcoma; and Bashford has met with mixed-celled sarcoma of the submaxillary gland. Several cases of Hodgkin's disease in swine have also been reported.

1 *Veterinary Journal*, 1902, p. 170.
2 For report of a large condylomatous tumour of the vagina of a young cow, *vide* Waghorn, *Veterinary Journal*, May, 1905, p. 253.
3 Virchow has described and figured a case ("Path. des Tumeurs," t. i., 1867, p. 337).
4 *Journ. of Comp. Path.*, etc., 1902, vol. xv., p. 155.
5 *Journ. of Comp. Anat.*, etc., 1904, vol. xvii., p. 64.
6 *Journ. of Anatomy*, vol. xxii., p. 420.
7 *Journ. of Comp. Path.*, etc., 1903, vol. xvi., p. 55.
8 *Clinical Journal*, June 11, 1902, p. 125.
9 *Arch. f. path. Anat.*, Bd. cxvii., S. 422.

Published records of non-malignant tumours in swine are even more scanty, than those concerning malignant tumours. "Fibroids" have been discriminated in the uterus and vagina, and in the latter organ Wolffian duct cysts occasionally occur. Papillomatous tumours of the intestine, exostosis of the ischium, bothryomycetic pseudo-plasms, hydatid cysts of the liver, etc., and goitrous tumours of the thyroid, have also been noted.

Swine are but moderately prone to tubercle.

## Sheep.

Sheep are unquestionably much less prone to malignant tumours than any of our common domesticated animals; indeed, Sticker's list of 1,170 of these tumours, comprises only 7 from sheep: of 6,800 sheep slaughtered during four years at Halifax, only one instance of malignant tumour was found.[1]

Of the few recorded cases, in the great majority the liver was the site of initial manifestation; other parts affected being the maxillary bones, eye, orbit, lung etc.

Examples of intra-ocular and orbital malignant tumours have been described by Axe and others; and a specimen of this kind is in Guy's Hospital Museum.

An example of "spina ventosa" of the inferior maxilla, owing to the growth of central sarcoma, is preserved in the Edinburgh Anatomical and Pathological Museum (No. 6 : 487); and the Cancer Research Staff has lately examined a specimen of ossifying sarcoma of the same bone.

Sharp[2] has published an account of a large cystic myxoma attached to the colon.

With regard to non-malignant tumours, very few modern instances have been recorded. Ovarian cystomata occur, a specimen weighing 7 pounds having been met with. Polycystic disease of the kidneys has also been recognized, and there is a specimen of this kind in the Hunterian Museum. In this connexion, it is of interest to note the occurrence of polycystic disease, affecting concomitantly several internal organs as well as the kidneys—*e.g.*, liver, lungs, and even the cardiac musculature, of which Cruveilhier has reported examples. Eve[3] has seen a cyst, connected with the undescended testis of a sheep with hermaphroditic malformation. Fatty tumours are stated to be met with in sheep, but I cannot cite a modern instance, unless the curious case described by Paget,[4] be so regarded. Here a mass of fatty outgrowths surrounded the outside of the heart, and processes were embedded in its substance, some of which even projected into its cavities.

Papillary growths and cutaneous horny excrescences are met with: some remarkable examples of the latter have been recorded, *e.g.*, a horn connected with the throat, weighing 26 pounds, and a similar formation of the flank 3 feet in length.

[1] J. F. Hodgkinson. *Journ. of Comp. Path.*, etc., 1903, vol. xvi., p. 269; a case of cystic cancer of the liver.
[2] *Journal of Anatomy*, 1896, vol. xxx., p. 559.
[3] Transactions of the Pathological Society, London, 1889, vol. xl., p. 463.
[4] "Surgical Pathology," 1853, vol. ii., p. 93.

Many instances of dermoid cysts are preserved in museums. A piliferous formation of this kind, replacing one of the kidneys, of which there was no trace, is in the Hunterian Museum; it contained masses of rolled-up wool, oily and fatty matters (No. 1,904, Pathological Series): another specimen, in the Hunterian Museum at Glasgow,[1] is described as: "cyst from a sheep's leg; a long spindle-shaped cyst, with fairly thick walls, covered internally with fine hairs; it is filled with balls of tightly compressed hairs, which had grown from its surface, shed, and accumulated gradually." Other examples of these formations are contained in the London Hunterian Museum; and two tumours of this kind, derived from a single animal, are there preserved (Nos. 159 and 160, Pathological Series).

In the teratological series of the same museum (No. 373) is a preparation showing a lock of wool, growing from a dermoid patch on the ocular conjunctiva.

Here also may be mentioned the occurrence of aberrant teeth in cysts and fistulæ of the neck, between the angle of jaw and external auditory meatus; which seem to arise from defective closure of a branchial cleft, with indications of a tendency to the formation of a redundant rudimentary mouth. An example of a dentigerous cyst of the upper jaw of a young sheep, associated with a malformed central incisor, may be seen in St. Bartholomew's Hospital Museum (1 : 119*a*).

Among the pseudo-plasms of sheep, reference must be made to coccidial tumours, such as those described by Nocard[2] in the intestine.

Tubercle occurs in sheep, and even in goats; and not so very rarely.

## Goat.

Eggeling[3] has reported a case of mammary cancer in a female goat (*Capra hircus*).

A curious form of quasi-malignant tumour of the anus of female Angora goats imported from South Africa, has been described by De Korte;[4] which strikingly illustrates the difficulty of discriminating certain tumours in animals from mycotic pseudo-plasms; for, while the author regards this malady as a true malignant tumour, other pathologists describe it as a granuloma.

Goats are certainly very rarely attacked by malignant disease; indeed, the above are the only modern examples of the kind known to me. Large odontomata, in connexion with the jaws, have been met with; and these have sometimes been described as sarcomatous. Cutaneous horns, and hydatid cysts, also occur in goats.

## Deer.

Deer seem to be as little liable to malignant tumours as goats. Otto refers to melanosis in a stag, but I cannot cite a single modern instance. In the museums, one finds specimens of fibroma of the antler, piliferous

[1] "Catalogue of Hunterian Museum, Glasgow," 1900, p. 393.
[2] *Journal of Pathology*, etc., 1893, vol. i., p. 404.
[3] Cited by Sticker, *Arch. f. klin. Chir.*, 1902, Bd. lxv., p. 661.
[4] Transactions of the Pathological Society, London, 1905.

dermoid of the conjunctiva, exostosis of the skull, ossiform tumour from the brain, bony deposits in the omentum, hydatid cysts etc.

## Rabbit.

Malignant tumours are certainly of extremely rare occurrence in these animals; indeed, hardly any really reliable case records exist. *Per contra*, rabbits are so exceedingly subject to psorospermosis, with its attendant tumour-like lesions, that—in tame animals—this malady may be said to be universal.

A few years ago Lack[1] claimed to have succeeded in experimentally producing cancer in a rabbit, the uterus being one of the structures implicated.

Lack's experiment has since been repeated by many pathologists, but no one has succeeded in reproducing similar morbid appearances.

Shattock,[2] having had occasion to examine the body of a rabbit that had been killed as obviously diseased, found a curious tumour-like, cystic, villous new formation, having the general aspect of a "chorionic mole," invading both uteri. Histological examination revealed the structure of papilliferous columnar-celled epithelioma. Similar formations were found in the peritoneum. The author regards this tumour as an example of spontaneous uterine cancer; and suggests that, in Lack's case, the disease probably had similar origin.

In the absence of special examination directed to the exclusion of psorosperms, it seems undesirable to accept these cases, as being scientifically verified examples of uterine cancer in the rabbit; and further observations are needed to establish the occurrence of this condition in these animals.

The Museum of the Royal College of Surgeons of Ireland contains a specimen[3] of "fungus hæmatodes" of the dorsal surface of the scapula of a rabbit—a firm, elastic, nodular tumour, larger than a goose's egg, being displayed.

Rabbits are also liable to melanosis. Lubarsch[4] has lately described a large renal tumour in a rabbit.

## Mouse.

Until the many various parasitic pseudo-plasms, to which mice and rats are specially prone, have been more thoroughly studied and discriminated, it will be impossible to form a reliable conclusion as to the incidence of true tumours in these animals.

Independently of the so-called "Jensen's tumour" and its variants, the nature of which will be discussed in a subsequent chapter,[5] several instances of malignant tumours in mice have been reported.

[1] *Journal of Pathology*, 1900, vol. vi., p. 154.
[2] Transactions of the Pathological Society, London, 1900, vol. li., p. 56.
[3] D. f. 511.
[4] *Cent. Bl. f. allg. Path.*, etc., 1903, vol. xvi., p. 9.
[5] Chapter VIII.

Even as far back as half a century, Crisp[1] exhibited at the London Pathological Society a malignant tumour of the pectoral muscle of a wild mouse, caught in a trap.

According to the Cancer Research pathologists, 11 cases of malignant disease were met with in 27,000 mice examined; and they seem to be of more frequent occurrence in tame than in wild varieties.

Tumours of this kind have been met with in the mammary region, skin, jaw, intestine, lung, vulva etc. Mice are also subject to melanosis. Haaland has described chondro-sarcoma; and Ehrlich chondroma.

Tyzzer[2] has reported instances of two independent growths in the same mouse—*e.g.*, cylindrical epithelioma of the lung, concomitant with adenoma of the kidney etc., and other examples of so-called "spontaneous" tumours.

With regard to the non-malignant tumours of mice, the published records known to me are exceedingly scanty: Spencer[3] has described an instance of "hornifying excrescence" of the head of a wild mouse; Treves[4] a similar formation on the neck; and other examples of this kind may be found in the museums. Various forms of adenoma and cyst-adenoma have also been reported.

Quasi-malignant growths due to parasitic sporozoa, blastomycetes, bacteria, pseudo-tuberculosis, nematodes etc., often occur;[6] and sometimes these pseudo-plasms also mimic non-malignant tumours.

According to Lydia Rabinowitsch, mice and rats are prone to tubercle, infected animals readily conveying the disease to others of their species.

### Rat.

As might be expected *a priori*, there is great similarity with regard to neoplastic proclivity, between rats and mice.

Malignant epithelial and connective-tissue tumours, do undoubtedly occur in rats, but they are very rare.

A good example of ossifying sarcoma of the leg bones of a rat, has been described and figured by Bland-Sutton;[5] and these animals are also liable to melanosis.

The epidemic occurrence of so-called "cancer" in rats, as well as a contagious form of the malady transmissible from one animal to another by implantation, as in the case of mice, have also been reported by several pathologists—*e.g.*, Hanau, Eiselsberg, Loeb, Velich, etc. The claim of these pseudo-plasms to be regarded as true malignant tumours has yet to be substantiated; all the indications at present available seem to me to point rather to their affinity with the granulomata and "infective epithelioses," to which rats are as prone as mice.

Here mention may be made of the fact that tumours of this kind

[1] Transactions of the Pathological Society, London, 1854, p. 348.

[2] *Journal of the American Medical Association*, October 20, 1906, p. 1237; Fourth Rep. Croft Cancer Commission, Boston, U.S., 1907, p. 27.

[3] Transactions of the Pathological Society, London, 1890, vol. xli., p. 402.

[4] Transactions of the Pathological Society, London, 1888, vol. xxxix., p. 463.

[5] *Journal of Anatomy*, vol. xix., p. 456.

[6] For instances experimentally produced, *vide* Chapter X.

have been produced in rats, by inoculating them with certain pathogenic yeasts (Busse, Curtis, Sanfelice, Wlaeff etc.).

Non-malignant tumours seem to be almost as uncommon in rats as in mice. An example of subcutaneous fibroma of large size, has lately been reported by Lecéne and Esmonet;[1] and in a pied rat, Bland-Sutton[2] met with a similar tumour in the neck; Shattock[3] has described adeno-fibroma of the mamma of a male pied rat; Loeb[4] adenoma of the mamma of a female rat; and Bland-Sutton ovarian hydrocele.

## Other Mammalian Animals.

An interesting instance of columnar-celled epithelioma of the ileum in a *lion* has been described by Harrison:[5] this animal was born in the Clifton Zoo, and passed the sixteen and a half years of his life in a comparatively small cage there, his general health having been good. He died after a lingering illness, marked by progressive wasting. Post-mortem examination revealed a circular cancerous growth, constricting the lumen of the bowel, just above the ileo-cæcal valve, which on microscopical examination had the structure above mentioned.

An example of cancer, in an aged lioness, has been reported by Welsh, of Sydney, New South Wales, who has also met with an instance of the same disease in an old *tigress*.

Cystic tumours of the liver, and exostoses of the vertebræ and other bones, have also been noted in lions; as well as rounded bodies, like detached fibromyoma, loose in the peritoneal cavity.

In the Glasgow Hunterian Museum,[6] is a portion of a *leopard's* stomach, with a necrotic fibroid tumour projecting beneath the mucosa; and Bland-Sutton has met with cystic disease of the ovaries in a tigress.

Many years ago, E. Rousseau reported that malignant tumours were "not infrequent," among the white *bears* confined in the Jardin des Plantes at Paris.

An instance of cancer of the stomach of a *rhinoceros* has lately been cited by Renshaw.

A large spongy exostosis, invading the superior maxilla and adjacent bones of the skull of a *hippopotamus*, has been seen by Otto; and, by the same pathologist, odontoma of the *elephant's* tusk.

Thick-walled cysts of the liver of the *porpoise* and *camel*, sometimes calcified, are preserved in museums.

A cancellous bony outgrowth from the inferior maxilla of the Virginian *opossum* is in the Hunterian Museum; which also comprises two subcutaneous dermoid cysts, with steatomatous laminated contents, one from the back and the other from the abdominal region of the same animal.

Multiple myomata of the uterus of a kind of *beaver* (*Myopotamus coypus*), have been described by Hilgendorf and Paulicki.

[1] *Bull. et mém. Soc. Anat.*, Paris, 1905, vol. lxxx., p. 38.
[2] *Op. cit.*
[3] Transactions of the Pathological Society, London, 1893, vol. xliv., p. 229.
[4] *Journal of Medical Research*, 1902, vol. viii., p. 46.
[5] *Op. cit.*
[6] Anatomical and pathological collection (34 : 15).

Whales are subject to warty outgrowths of the skin, which are often due to parasitic *cirripedia;* as described by Weltner.

A malignant renal tumour (derived from an adrenal "rest"), has been described by Bland-Sutton in a *marmot;* the same author has also met with odontoma in this kind of animal; and Otto has seen "spina ventosa" of the inferior maxilla.

Even in marsupial animals, a few instances of malignant and other tumours, have been reported.

In the Hunterian Museum (No. 1,038, Pathological Series) in one half of the inferior maxilla of a *kangaroo*, distended by a large central ossifying sarcoma; and, according to Otto, specimens of "spina ventosa" and exostoses, in marsupial animals, may often be seen in museums.

Examples of intra-abdominal lympho-sarcoma in dasyures, have been described by Eve and Bland-Sutton; while, the latter author, has also seen cancer of the marsupial pouch of a short-headed phalanger.

## Birds.

It is stated by Pick and Poll, that malignant tumours are of very rare occurrence in birds; but, if this is meant to apply to the common domesticated kinds, it cannot be accepted as quite accurate; for, as Heusinger long ago pointed out, malignant tumours are not so very uncommon in these, and this is quite in accord with modern indications.

The common domestic hen seems to be remarkably prone to sarcoma, instances having been reported by Hathaway, Patterson, Birchmore, Crisp, Parker etc.; melanosis also occurs. Squamous-celled epithelioma of the floor of the mouth has been described by Pick; an enormous quasi-malignant ovarian tumour by Bland-Sutton; and two instances of epithelioma of the small intestine by Ehrenreich and Michaelis.

A large fibro-cartilaginous tumour, from the subcutaneous tissue of the thigh of a domestic fowl, is to be found in the Museum of the Royal College of Surgeons of Ireland; and a large fatty tumour was removed from the pectoral region of a hen by Crisp. Ehrenreich and Michaelis have described two examples of fibroma of the mesentery. Exostoses, hyperostoses, and ossified tendons, are not particularly rare; while sebaceous cysts, hornifying outgrowths, warts, and even corns, are fairly common.

Large cystomata of the hen's ovary are often met with, as the specimens in many museums testify.

Mougie has seen a large serous cyst of the abdomen of a hen; and dermoid cysts, containing feathers, also occur.

A quasi-sarcomatous tumour from the lung of a Bernicle *goose* is preserved in Guy's Hospital Museum (No. 1,793, Pathological Series). In the Museum of the Irish College of Surgeons (D. f., 56), is an immense "fibroid" tumour, "as big as a large melon," which occupied nearly all of the greatly distended abdominal cavity of a goose; this tumour was so slightly attached that, when the abdomen was opened, it fell out, so that its exact point of attachment could not be determined, but it was surmised to have originated from the oviduct or intestine. Harrison[1]

[1] *Bristol Med.-Chir. Journ.*, 1894, vol. xii., p. 288.

met with a similar tumour, which weighed at least one pound, in an ancient goose supposed to be over thirty years old, which died in the Clifton Zoo; and in this instance the pedicle of the tumour was connected with the mesentery. A large, lobulated, quasi-fibrous tumour, from the neck of a goose, is in the Hunterian Museum (No. 307, Pathological Series). Dermoid cysts, containing feathers, have also been found in these birds.

Other examples of tumours in birds of which I have cognizance are:—A subcutaneous round-celled sarcoma, of yellow colour, of the wing of a dove (Woods Hutchinson); alveolar sarcoma of the pectoral region of a golden plover, in the Hunterian Museum; malignant tumour of the pectoral region of a canary (Crisp); "fungoid" tumour of the eye of a canary (Crisp); "spina ventosa" of the great wing-bone of a parrot, cited by Otto; myxo-sarcoma of the pectoral muscles of an Indian parakeet (Bashford); malignant tumours among the carnivorous birds of the Paris Jardin des Plantes, noted by Rousseau; ovarian tumour in a pheasant, by Slater; large sebaceous cyst of the pectoral region of a pigeon, in the Irish College of Surgeons' Museum; I had a thrush which developed a similar cyst on the head, whence sprang a horn-like outgrowth; and formations of this kind have been seen in other birds (dove, canary, partridge); fibroma of the thigh of a grouse in the Hunterian Museum; the oldest inhabitant of the Clifton Zoo, a griffin vulture, was subject to an exostosis of the foot, as reported by Harrison; turkeys seem to have special proclivity to large ivory exostoses of the bones, of which there are specimens in the Hunterian and other museums, to which J. Hutchinson[1] has specially called attention; on each metatarsal bone of a young rhea Bland-Sutton found an enchondromatous tumour; among the Hunterian preparations in the English College of Surgeons' Museum, is: "A tumour from the belly of an ostrich" of fibro-cellular structure; also an exostosis on a cervical vertebra of the same bird; and a cyst developed from an unobliterated vitello-intestinal duct, attached to the intestine of an emu.

Contagious tumour-like lesions due to tubercle, psorospermosis and other parasitic infections are common in birds. To this list the contagious inoculable malady called *Molluscum contagiosum*, especially prone to occur in fowls and pigeons, must be added; and its similarity with the like-named malady of human pathology is also noteworthy.

Birds are as a class very prone to tubercle, especially the common domesticated kinds.

### Reptiles and Amphibians.

With regard to these groups of animals all that can be said is, that malignant and benign tumours are known to occur among some of their members. By systematic post-mortem examination of the bodies of salamanders from the Berlin Biological Institute, Pick and Poll[2] have demonstrated cystic glandular cancer of the testis of the giant salamander (*Crypto-branchus japonicus*). These pathologists have also found a benign tumour, which they regard as thyroid adenoma, growing from

[1] *Archives of Surgery*, 1893, vol. iv., p. 121.
[2] *Berlin. klin. Woch.*, 1903, No. 23, S. 518; No. 24, S. 546; and No. 25, S. 572.

the neck of the snake-necked tortoise ; and also a tumour, as to the nature of which they are doubtful, growing from the left side of the neck of a *Salamandra maculata*. Plehn[1] has collected records of other cases of tumours in salamanders, lizards, and frogs.

A specimen of columnar-celled cancer of the kidney of a frog (Smallwoods), has been verified by the Cancer Research Staff.

An interesting example of cancer of the ovaries with widespread dissemination, in a python, that had lived for fifteen years in the London Zoo, where it died cachectic on account of this ailment, has been described by Bland-Sutton ;[2] and this author has also met with multiple chondromata, in a rachitic Indian lizard, from the same collection of animals.

Sarcoma in a frog has been reported by Murray ; and Gebhardt has investigated two pyloric tumours in frogs, due to protozoa.

Otto has seen " spina ventosa " of the caudal vertebræ of a chameleon ; and there is a specimen showing exostoses on the ribs of a chameleon, in the Hunterian Museum (No. 797).

Sandifort has met with exostoses on two vertebræ of a boa-constrictor.

## Fish.

We have to note the great proclivity of fishes to parasitic infections of various kinds (sporozoa, mycoses, bacteria, nematodes etc.), many of which cause large swellings, which resemble malignant tumours.[3] Epidemics among river fishes (barbel, pike etc.), due to parasitic myxosporidia, have been noted in Germany ; and this form of disease is common in the pike's bladder.

From a crowd of parasitic pseudo-plasms, the Cancer Research Staff claim to have demonstrated sixteen examples of true malignant tumours in fishes, some of them pelagic ; but, long before this body took the matter up, instances of malignant tumours in fish had been reported, especially in carp, by Crisp, Bland-Sutton, Sibley, Ohlmacher, and others.

Carp have been kept, under artificial conditions, from the remotest times ; and, it is not without significance, that just this fish should have furnished so many examples of malignant tumours.

A sarcomatous tumour from a golden carp, has been described and figured by Bland-Sutton,[4] from a specimen in the Hunterian Museum ; a similar tumour of much larger size, also in a carp, had previously been described by Crisp ;[5] examples of malignant epithelial tumours in carp have been reported by Battaillon,[6] and Bashford.[7] Sibley,[8] having examined a specimen labelled " multiple sarcoma of a carp " from a German pathological museum, found that the tumours consisted almost entirely of psorospermia.

[1] *Zeitschr. f. Krebsforschung*, 1907.
[2] *Journal of Anatomy*, vol. xix., p. 464.
[3] For some interesting remarks on this subject, *vide* Gurley and Tyzzer, "Tumours and Sporozoa in Fishes," First Annual Report of the Cancer Committee, Harvard Medical School, Boston, U.S., October, 1900, etc.
[4] *Journal of Anatomy*, vol. xix., p. 447.
[5] Transactions of the Pathological Society, London, vol. v., p. 347.
[6] *Zeits. f. Fleisch. u. Milch.-Hyg.*, 1898, S. 151.
[7] Scientific Reports of the Cancer Research Fund, 1905, No. 2.
[8] Transactions of the Pathological Society, London, 1890, vol. xli., p. 322.

Lately, several instances of "cancer epidemics" in trout, have been reported by Pick, Scott, Gilruth, Bashford etc.; and, in all these cases, the fish had been long kept under artificial conditions in special "hatcheries."

Two examples of malignant tumours from fish (cod, gurnard), which had lived under natural conditions, have also been studied by the Cancer Research Staff;[1] and Ohlmacher has seen sarcoma of the peri-vertebral connective tissue, with metastases, in a lake pike.

Curious tumours due to sporozoa, in a minnow (*Cyprinus phoxinus*), have been described by Davaine; and, in a stickleback (*Gasterosteus trachurus*), by L. Tait; while, in the Hunterian Museum, is a dace (*Cyprinus lenciscus*), the surface of whose body is covered by "a mycoderm confervoïd growth" (No. 2,305).

A striking feature in the neoplastic pathology of fishes, is the great frequency of exostoses and bony tumours, which are generally multiple.

In the chief pathological museums, many specimens illustrating the proneness of codfish to multiple exostoses and bony tumours are to be found;[2] their seats of election are the vertebræ, superior maxilla, tail etc. In the stomach of these fish, submucosal "fibroid" has been met with; and a similar tumour has been found in the subcutaneous connective tissue. Specimens of the sclerotic of the eye of a codfish, exhibiting numerous white nodules, due to parasitic gregarinæ, are preserved in the Glasgow Hunterian Museum (39 : 32). As previously mentioned, spindle-celled sarcoma of the air-bladder of a codfish, has been investigated by the Cancer Research Staff; also intra-abdominal glandular cancer in a gurnard.

Multiple bony tumours of the skeleton of some chætodons are of such common occurrence that W. Bell, who first specially called attention to them, rather rashly concluded that they were "natural" in this fish.

Large bony tumours of the occipital region of the skull etc. are also often met with in *Ephippus gigas* and *faber*, as reported by Valenciennes.

Otto long ago called attention to the frequency of large exostoses, connected with the spines of the vertebræ of scabbard fish (*Lepidopus peronii* etc.), and of the spiny fish (*Sparus erythrinus*); Gervais has since confirmed and extended these observations, describing a large bony outgrowth from the occipital crest of *Pagrus unicolor*.

Exostosis of the jaw-bone of a pike has also been described.

The Anatomical and Pathological Museum of the College of Surgeons of Edinburgh (5 : 172*b*), contains a specimen showing extreme hyperostosis of many caudal vertebræ, from a haddock; and, in the Glasgow Hunterian Museum, a portion of one of these fishes is exhibited, so as to display the innumerable colonies of psorospermia parasitic in its flesh (39 : 33).

[1] Scientific Reports, No. 1, 1904, p. 7.
[2] Glasgow Hunterian Museum, Nos. 5, 172, and 172*a*; and in the London Hunterian Museum, Nos. 796 and 1,039.

## CHAPTER VI

## TUMOURS IN VEGETABLE ORGANISMS

In this chapter I propose to show: (1) that tumours, analogous to the malignant and non-malignant tumours of human and animal pathology, occur also in vegetable organisms; (2) that such tumours are dervied from abnormally evolving buds; and (3) that in the vegetable world tumour-like formations are of very common occurrence, as the consequence of parasitic and other irritants *ab extra.*

### Bud Formation and its Anomalies.

The process of gemmation in plants is of great importance, for the understanding of their development and organization; and it is capable of throwing much light on the analogous processes in animal and human ontogeny, to which biologists and pathologists have hitherto paid far too little attention—for gemmation has its pathological as well as its physiological outlets. The simplest buds consist either of single undifferentiated cells, or of groups of such cells derived from single cells, the differentiated tissues of the parent plant having no share in the formation of the primitive bud, and no connexion with it until a later period.

Usually buds develop in organic connexion with the parent stock; but sometimes, as in the tiger-lily, they fall off and develop separately (bulbils). The branch-bud here acts like a seed-bud, but is capable of developing without fertilization. Hence buds artificially separated, may be used for purposes of propagation, as in the familiar processes of grafting, budding, layering, etc. Thus, each bud is potentially a new individual having, under favourable circumstances, the power of evolving into a perfect organism.

But the degree of development actually attained, usually falls far short of this; for, owing to disturbances in nutrition, buds may be variously modified in adaptation to other ends. Thus, in extreme cases, they may remain permanently undeveloped; or they may remain for long periods, even for years, in a dormant or latent state; and yet, under favourable conditions, their activity may revive.

When their development is somewhat less restricted, the products may be dwarfed, or evolved into spines, tendrils, twigs, or various irregular formations, which may properly be called tumours.

In the higher vegetable organisms buds are usually distributed with great regularity, being either terminal or axillary; buds arising in any other way, are said to be of adventitious origin.

Now, adventitious buds differ from normal buds only in respect to position ; for, they originate otherwise in precisely the same way, as those normally formed on the axis. Adventitious buds have been found on almost every part of plants. They sometimes develop in extraordinary numbers on the stems and branches of trees, owing to some interference with the vegetation of the normal buds ; and they may be evoked by wounds. When a begonia leaf is placed in damp soil, and incisions are made across its "nerves," buds spring from every incision ; and as many fresh plants may be obtained in this way as the leaf has received wounds. The Dutch bulb growers have cleverly availed themselves of a similar property, to propagate hyacinths ; this they effect either by making two or three deep incisions into the base of the bulb—destroying the nascent flower-stalk—when, after a short time, numerous small buds form along the edges of the cut surface ; or, by scooping out the interior of the base of the bulb, and so leaving exposed the cut ends of the sheathing leaves, from which buds soon spring in great numbers.

Leaves subjected to slight pressure, and in process of decay, frequently develop buds in a similar way.

Degrees of injury which fall far short of this, such as those produced by various mild irritants, as described by Waldenburg, cause local thickenings, owing to increased growth and proliferation of the cells of the part.

In like manner, as will be seen in the sequel, the various kinds of galls arise.

In a general way, the root is distinguished from the stem by the absence of buds ; but, under exceptional circumstances, adventitious buds may form even on roots. Duhamel, having planted a willow with its branches in the ground and its roots in the air, saw its roots become covered with leaf-bearing buds, while the buried branches produced roots. The production of a flower-bud has been noticed on the root of a species of Impatiens. In some cases, the divided root suffices for the reproduction of the entire plant, as in the Japan quince, the Osage orange, and especially the Paulownia—the roots of which, even when cut into small pieces, can develop into perfect trees.

There are many plants which produce buds on their leaves. This is of much commoner occurrence among the lower orders, and the ferns, than with the *Phanerogamia*. As examples among native plants may be instanced the watercress, *Cardamine pratensis*, and *Malaxis paludosa*—in the last named, the buds are known to be derived from single cells of the surface of the leaves. Begonias exhibit this power in a remarkable degree ; in some instances, single scales from the leaves or stem habitually develop into young plants. One of the best-known instances is that afforded by *Bryophyllum calycinum*, a succulent tropical plant, whose leaves produce buds furnished with roots, stem, and leaves, at the extremities of its lateral nerves. These buds, which fall off spontaneously and root in the earth, may be compared to ovules which do not need to be fertilized before developing ; and the leaf of the *Bryophyllum* may be regarded as an open carpel, in which the seeds have been developed by nutritive action alone. Consideration of the subject in this light, leads us to regard the bud as an individual vital centre resembling the ovule. Many facts in vegetable physiology and pathology confirm this view. Schleiden regarded the ovule as a modified bud, and the now well-authenticated cases of parthenogenesis in plants support his theory. In these cases, new individuals are developed from unimpregnated ovules, as from buds, the defect in the ovular reproductive power, which ordinarily renders impregnation necessary, being removed. The ovule or seed-bud, then, differs from the branch-bud essentially only in this : that it generally needs for its development the fertilizing influence of the pollen. The fecundity of Bryophyllum, completes the analogy between the bud and the fertilized ovule. According to Hofmeister, the buds of Bryophyllum arise before the complete unfolding of the leaf, as small masses of undifferentiated parenchyma, in the deepest parts of the crenations of the leaves.

Buds thus arising, may take root and give origin to leaf-bearing branches, while still in connexion with the parent plant, as in *Drosera*

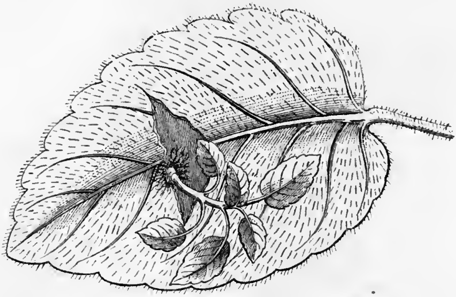

Fig. 1.—An Adventitious Leaf-bearing Shoot developed on a Leaf of Episcia Bicolor (Masters).

*intermedia*, *Episcia bicolor* etc. (Fig. 1), though they generally develop more readily after the leaves have fallen off. Adventitious buds have also been found on the petiole, lamina, stipule ; and, in short, on every part of the leaf. It thus seems as if buds may arise wherever undifferentiated cells, still capable of growth and development, are present.

Such facts as the foregoing show, that there is no specific distinction between somatic and germ cells, as Weismann has maintained ; they indicate that the reproductive properties manifested by somatic and germ cells are the same in kind, and that they differ only in degree. In short, the whole history of gemmation in plants, testifies against fundamental difference between somatic and germ cells.

It seems probable that the capacity of the higher vegetable organisms, for manifesting these anomalous kinds of bud formation, may be due to reversion ; at any rate, they remind us of the proliferous outgrowths so common among the *Thallophyta*.

The shoots which spring from buds usually develop into structures of the same form, as those which compose the parent plant; but, it occasionally happens, that particular buds develop differently from others of the same stock. Gardeners call these changes "sports"; by Darwin they were described as "bud variation"; while De Vries discriminates all abrupt transformations of this kind as "mutations." The common moss-rose is considered by Darwin to have originated in this way from the Provence rose.

Not only normal, but adventitious buds as well, are liable to this kind of mutation. Fronds of the same fern, for instance, often manifest striking morphological variations; of this a remarkable example is figured below (Fig. 2), which represents a portion of a frond of *Pteris quadriaurita* bearing an adventitous bud, whence foliage—very different from that of the rest of the plant—has emerged. Mutations of this kind, are of

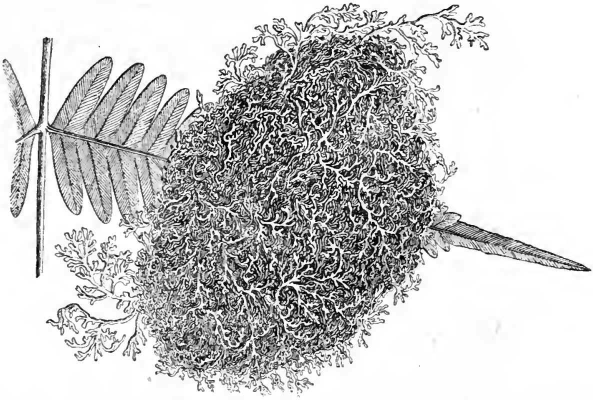

FIG. 2.—PORTION OF A FROND OF PTERIS QUADRIAURITA, IN WHICH THE FOLIAGE EMERGING FROM AN ADVENTITIOUS BUD IS VERY DIFFERENT FROM THAT OF THE REST OF THE PLANT (MASTERS).

much commoner occurrence among the lower than among the higher orders of plants; and among cultivated than among wild species.

Many mutations were regarded by Darwin as due to reversion; others he ascribed to the so-called "spontaneous variability," understanding by this term variation of which the causes were not obvious.[1]

In formulating the doctrine of natural selection, which is peculiarly his own, there can be no doubt that Darwin failed to attach due weight to the occurrence of mutations independently of selection and of adaptation. It has since been shown that numerous variations of this kind do occur, some of which are obviously disadvantageous to their modified possessors, while others are neither advantageous nor disadvantageous.

It is with these mutations that the various pathological new formations should be classed. Here brief reference must be made to the conditions

[1] According to H. Spencer: "Spontaneous variations are interpretable as results of miscellaneously compounding the changes wrought in different lines of ancestors by different conditions of existence."

which determine the incidence of gemmation, gamogenesis, and alternation of generations; and, it will suffice for our immediate purpose, if I state that the conclusion derived from the consideration of the ensemble of this important subject is, that the outcome of growth in any particular case is mainly determined by nutrition. Thus gemmation or asexual multiplication may be regarded as the outcome of favourable nutritive conditions, resulting in vegetative growth; while gamogenesis is likely to ensue when these conditions are less favourable. From this standpoint, gemmation and tumour formation in the higher organisms, are instances of reversion from dominant gamogenesis to the asexual process; and the genesis of malignant and other tumours is a phenomenon of the same order as discontinuous growth in general.

Thus the origin of buds, as well as their subsequent development, is chiefly determined by the conditions of nutrition. Wherever there is an excess of nutritive materials, capable of being utilized for growth by the cells of the part, there buds may arise.

## Vegetable Tumours and Gemmation.

From the consideration of these interesting processes, we must now pass to the closely allied subject of vegetable tumours; which, as I shall proceed to show, are the outcome of abnormal bud evolution.

We shall find that in these cases, the local changes are modelled after the processes of normal growth, and that both are subject to the same laws. Changes of nutrition, causing altered growth and impaired development, seem to be the common ætiological factors underlying all of these abnormal formations.

Their physiological prototypes must be sought in such kindred processes, as those above described. The clear recognition of this important truth is likely to lead to great results, in the future development of this branch of pathology.

I think there can be no doubt that the neoplastic process can be more satisfactorily studied in plants than in animals, owing to the absence, in the former, of many factors—such as nerves and bloodvessels—which, in the latter, complicate and obscure the essential nature of the process. In plants, the early animal embryo, and in the lower animals, all the phenomena of growth go on without either nerves or bloodvessels. And so it is, at the outset, with all morphological variations, including bud, cancer, and tumour formations. In all these cases the nerves and bloodvessels have not the slightest direct influence.

By bearing in mind these simple but fundamentally important considerations, we are at once able to get rid of that incubus of nineteenth-century tumour pathology—the Broussaisian doctrine—which regards tumour formation as an outcome of "inflammation," rather than as an anomaly of growth; for, in the vegetable world, as in the lowly organized part of the animal kingdom, "inflammation," in the proper sense of the term, is impossible, owing to the absence in these organisms of that co-ordinated lymph-vascular and nervous mechanism, which is the essential apparatus by which alone the phenomena of "inflammation" can be produced, as I shall have occasion to point out in the sequel.

My investigations as to the nature of tumours in trees have led me to classify them into three main groups.

The *first* group comprises those circumscribed woody nodules so commonly found beneath the bark of the beech, elm, oak, cedar, holly, and other trees, to which the vaguely used term "knaur" is commonly applied.

I have in my possession a typical example, on a small scale, from an elm-tree. An ovoid swelling, about the size of a Tangerine orange, projects beneath the bark of one of the branches. Its surface is devoid of buds and shoots. On section, it is seen to be composed of dense wood, covered with rather thickened bark. Examination of the cut surface shows that the tumour has been formed round two centres of development, each of which is surrounded by its own system of concentric woody laminæ. These concentric systems are embedded in other woody laminæ, derived from the investing cambium layer, and consequently disposed parallel with the axis of the branch. The nodules have thus been partially embedded in the woody tissue of the branch, and have lost their direct connexion with the cambium layer. A narrow ligneous pedicle connects

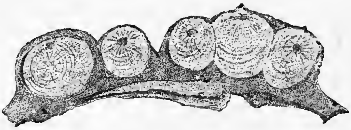

Fig. 3.—Showing Five Circumscribed Tumours in the Bark of a Holly-tree (Natural Size).

the tumour with the wood of the branch. At the free extremity of the tumour, it is interesting to observe a separate woody nodule, the size of a small pea, completely isolated in the cambium layer. This may be taken as illustrating an early stage in the development of such growths, which originate from disorderly evolving adventitious buds.

Mr. S. Paget has presented some good examples of these tumours to the Hunterian Museum, where they may now be seen. They are generally single, but occasionally several are found close together, as was the case in one of Paget's specimens, figured above (Fig. 3). This is described in the catalogue (No. 546A) as a portion of the bark of a holly-tree, with the cambium layer, and a small portion of the wood. Deep in the substance of the bark are five rounded tumours composed of hard wood, their cut surfaces showing faint concentric lamination. At the upper part of the specimen, three of these have partially coalesced. They are distinctly circumscribed in the surrounding tissues; and there are no signs of any pedicles connecting them with the wood of the tree. The succeeding specimen (No. 546B) shows a similar tumour from a beech-tree, also devoid of pedicle; and, in No. 546D, we have five similarly situated tumours, also from a beech-tree, with a few buds projecting from their surfaces, while here and there some of these buds have developed shoots or minute branches.

It may be said of these tumours, that they usually present as rounded or ovoid swellings in the deeper part of the bark, varying in size from a pin's head to a cocoanut or larger. The older nodules are generally found lying completely isolated in the bark; and a narrow fibro-vascular pedicle may sometimes be seen, connecting the younger ones with the woody tissues of the trunk or stem. When the pedicles persist, these formations are apt to become included in the woody tissue of the stem, giving rise to the so-called "knots" in the wood. In the earlier stages of their development, these tumours are occasionally surmounted by a small stunted branch or shoot. On section, they are found to consist of very dense wood, having a more or less concentric arrangement around one or more centres, according as their origin is from single or multiple buds. In most cases both pith and medullary rays can be made out. Not infrequently, however, their internal structure is much more irregularly disposed. In short, they comprise all the structural elements of the part whence they spring, but differently arranged. It would seem as if they might be regarded as stunted branches, in which the woody layers had been abnormally developed, in compensation for the curtailment in length and in other respects.

Lying at first isolated in the bark, these nodules increase in size at the expense of the surrounding nutritive materials. Hence, it often happens that their growth on the side of the cambium outruns that on the other side, where the nutritive supply is less abundant, so that a certain eccentricity in the arrangement of the laminæ is produced. Destruction of the bark which usually covers them in, whether as the result of injury or some other cause, such as pressure of the growing nodule itself, renders this tendency to increased growth on the side of the cambium still more marked; for, we then see complete cessation of growth at the exposed surface, which may even decay in consequence, while the side of the nodule next to the wood, owing to the proximity of the cambium, still continues to increase.

These tumours, as Dutrochet long ago discovered, first appear as very small buds in the cellular tissue of the bark; where they originate from unspecialized cells, quite independently of the wood of the trunk. In short, almost all of those who have specially studied this subject, are now agreed in ascribing the origin of these tumours to disorderly growth of adventitious or dormant buds. There is no doubt that buds may remain in a quiescent state for years; and then, under the influence of favourable conditions, develop renewed activity, the result being either a shoot, a branch, or one of these tumours.

Such being their origin, it is not surprising to find these tumours, like buds, possessed of distinct individuality; and capable of reproducing their like in the form of buds, shoots, branches etc. It even occasionally happens that, in their young state, these anomalous formations may be used for propagating the species asexually.

In all of the above instances, the outcome of the morbid process is the production of a highly organized, circumscribed, new formation, analogous to the fibromas, lipomas, and other similar non-malignant new growths of human and animal pathology.

Before entering on the consideration of the second group of tumours in trees, I must first of all offer a few observations with regard to certain intermediate formations of the nature of local overgrowths. I have often remarked in various trees the presence of hypertrophic branches; and, in several instances, I have seen localized hypertrophies involving the whole thickness of portions of the branches of such trees as the elm, lime, and oak. These conditions may be compared with the hyperostoses of human pathology. They occupy an intermediate position between the hypertrophic and neoplastic processes. Such conditions arise at an early stage of development, in consequence of excessive activity of the cambium at the affected part. These local overgrowths generally present as elongated protuberances covered with bark, their diameter being many times greater than that of the branch or stem whence they grow. On section, they consist of hard wood, the concentric layers of which are unusually thick and very obvious, while the medullary rays, extending from the centre to the periphery, are but thin. Trécul has figured a fine example of this kind from a birch-tree.

The *second* group, comprising the continuous tumours, are comparable with the exostoses of human pathology. These present as woody outgrowths of the trunk or branch. They often attain great size, as in the specimen figured on the next page (Fig. 4), which measured 16 by 11 inches, and weighed 67 pounds: the diameter of the branch on which this tumour grew, was 4½ inches on the proximal and 4 inches on the distal side.

The general characters of these growths may be gathered from the subjoined brief description of this specimen, which was removed from one of the largest branches of a young elm-tree—probably about thirty-five years old—on the main trunk of which was another similar growth, the tree being in other respects healthy. It was completely covered with rather hypertrophied bark, and two small branches grew from its surface near the periphery. On longitudinal section, it was found to consist of very hard wood, directly continuous with that of one side of the branch whence it grew. The laminæ composing the tumour showed a concentric arrangement of outcurved, irregularly wavy layers; while those of the branch itself appeared longitudinal (Fig. 4). Moreover, the former were many times thicker than the latter; and in the broadest part of the tumour I was able to count twenty-six of these layers. A singular feature in this case is, that a portion of the tumour had grown completely round the healthy part of the branch, outside the bark; and had then blended with the main tumour on the opposite side, so as completely to encircle the branch on which it grew. This specimen was removed from a tree growing in a damp meadow, where the soil was heavy, and saturated with sewage-polluted water. An adjacent elm, of about the same size, presented a single similar outgrowth on its main trunk.

Similar tumour-like growths have occasionally been seen even on the root of various plants—*e.g.*, *Taxodium distichum*, *Cupressus macarocarpa* etc.

Dutrochet describes these growths as arising in much the same way as the discontinuous knaurs, by a kind of bud formation, in the deeper part of the cambium layer; hence their connexion with the woody tissues of the stem is well secured from the outset, and so it is never lost. These tumours may be regarded as stunted, abnormally evolved, branches.

Composite tumours of this kind, resulting from a group of buds—instead of a single one—being concerned in the origin of the malady, are by no means unusual; and thus very dense formations are often developed on elm stems, which are in much demand by cabinet-makers, on account of the remarkable patterns presented by the diversely contorted arrangement of their woody fibres.

Such being their structure and mode of origin, the tumours of this group may fairly be compared with the exostoses and analogous continuous tumours of human pathology; and, like them, they are highly organized.

FIG. 4.—A CONTINUOUS TUMOUR—COMPARABLE TO AN EXOSTOSIS—FROM AN ELM-TREE, IN LONGITUDINAL SECTION.

In the *third* group, I include all those new formations, called by the French *broussins*, whose distinguishing peculiarity is the very free and continuous formation of proliferous buds, shoots, and stunted branches. The term "burr" might very well be employed as the English synonym for these growths, which often attain enormous proportions.

I have seen an old lime-tree, with a huge excrescence of this kind densely studded with buds, shoots, and brushwood, growing at the junction of the trunk with the main branches.[1]

Three other aged lime-trees in the immediate vicinity were similarly affected. In all of these cases, the general health of the trees appeared to

[1] This growth is figured in my book on "The Principles of Cancer and Tumour Formation," Fig. 15, p. 98.

have deteriorated considerably, as indicated by numerous dead branches, etc. In the same neighbourhood I have seen similar growths on elm, hornbeam, and other trees, one of which is figured on the next page (Fig. 5). The trees of this particular locality are, in fact, remarkably prone to these growths, and to various other morphological anomalies. Most of these trees are old, and of large size. For a long period they have been left quite uncared for—innocent of the acts of forestry. The situation of the locality is peculiar. It forms part of a shallow depression, lying below the slope of a hill. A large brook, the natural watershed of the neighbourhood, runs sluggishly through the low-lying part. In its course, it here forms several large lacustrine ponds, owing to the slightness of the gradient. The water is highly charged with sewage matter. Clay formation underlies the whole neighbourhood, and forms the bed of the watercourse, while a layer of loose gravel rests on the clay. It results from this arrangement, that the whole of the depressed area is thoroughly saturated with sewage-contaminated water; and its vegetation has consequently long been abnormally nourished.

A specimen illustrating the same type of disease, from one of the chief branches of a hornbeam-tree, is shown in Fig. 5. The growth is composed of innumerable, densely massed buds, a few of which have developed into shoots and twigs. Almost the whole circumference of the branch, for a distance of 15 inches, is surrounded by the growth. On section, the subjacent woody tissue of the branch, corresponding to the seat of the disease, is seen to be double its normal thickness. The wood here is very dense and of irregular formation, except in the central part; and, between the two, there is no definite line of demarcation. Interspersed in this dense wood are detached fragments of bark; and, in several places, long processes of bark penetrate deeply into the wood. This great thickening and irregular formation of the wood, are due to the exuberant and irregular flow of sap, caused by the abnormal and proliferous gemmation, which is the essential element of the disease.

I have seen similar tumours on elm and other trees.

The peculiarity of growths of this kind, consists in the immense number of buds which develop adventitiously in the cambium layer of the affected part; when, they either remain dormant, or forthwith develop into shoots or stunted branches. The aggregation of these structures causes retardation and irregularity in the flow of the sap; whence the exuberance of the growth, and the curious markings produced in the wood. Moquin-Tandon mentions having seen a grafted ash, in the Botanical Garden of Toulouse; where, below the graft, a large growth of this kind formed, from which proceeded over a thousand small, densely packed interlacing branches.

The production by these growths of large quantities of proliferous, lowly organized, cellular tissue, which subsequently undergoes some imperfect developmental changes—mimicking the structure of the part—constitutes the nearest approach in vegetable pathology to the malignant tumours of human and animal pathology. The absence in these vegetable tumours of anything like the disseminativeness of human malignant tumours, may be urged as an objection to this comparison. But to this the answer is, that in the absence of a highly specialized lymph-vascular system, capable of transporting the proliferous cells, such disseminativeness is not to be expected; and that it is to deficiency in this respect—rather than to any essential difference in the nature of the morbid process—that the absence of disseminativeness in vegetable tumours must be ascribed. For, as I have previously indicated, the essential feature of malignancy is not disseminativeness, but rather the indefinitely sustained activity of certain lowly organized cells, which grow and multiply independently, without ever reaching the highest grade of organization.

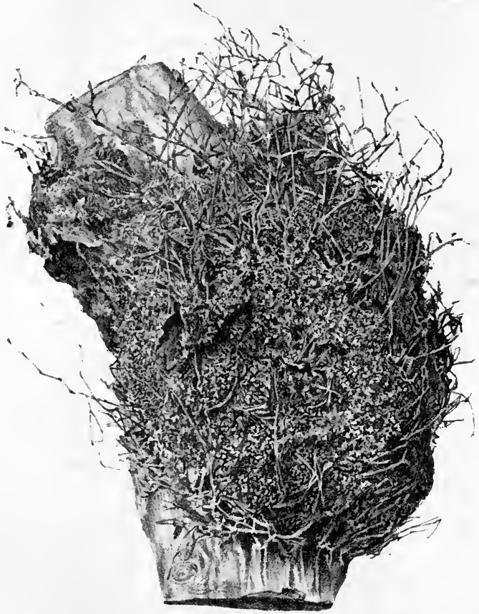

Fig. 5.—A Malignant Tumour, densely studded with Shoots and Stunted Twigs, from One of the Chief Branches of a Hornbeam-tree.

With regard to the ætiology of these growths, beyond what has been above indicated, all that I need now say is, that I have been unable to find any evidence as to their being due to parasites or other irritants *ab extra*.

### Galls and Other Vegetable Pseudo-plasms.

Even in human and animal pathology it cannot be denied, that irritative conditions may elicit formative reactions; and, in the vegetable world, even among highly evolved forms, reactions of this kind are of frequent occurrence as well as of marked character. This is exemplified in the case of galls, which may comprise not only structures similar to those met with in the parts whence they originate, but also other structures which do not occur there ; thus, as Beyerinck has shown, cells which are usually only developed in the bark, are frequently found in some leaf-galls etc.

The formation of galls is certainly a very interesting phenomenon, which has yet to be fully explained, as have also the analogous processes underlying bud, cancer and tumour formation, and other morphological variations.

It was formerly thought that galls arose in consequence of excessive local cell growth and proliferation, excited by a virus instilled into wounds made by insects in depositing their ova ; but the researches of Adler and Beyerinck have shown the inadequacy of this conception. They have conclusively proved that galls are due, not to the sting of the parent insect, but to the activity of the larva after it has been hatched.

Although most gall-producing insects do actually wound the tissues of plants in depositing their ova, yet no galls result from the lesions—for instance, in the case of the common oak-apple gall, the *Biorhiza aptera* deposits its ova in punctures in the bud early in the winter, but no gall formation occurs until the following spring, when the larvæ become active ; similarly, when no ova are deposited in the punctures made by the parent insect, no gall is formed ; and the result is just the same when, although ova have been deposited, the embryos fail to develop or die early ; and, when the larva dies, the gall ceases to grow. From these considerations it follows that the gall is the reaction of the plant to some stimulus proceeding from the larva, the nature of which is still under discussion.

It is hardly likely that the mere presence of the larva, acting as a foreign body, or its movements *per se*, can be the real causative factors of these formations, otherwise there would not be such extraordinary diversities in the resulting galls—those produced by the larva of each kind of insect presenting structural peculiarities which are quite *sui generis*. Thus, on the oaks of Central Europe alone, nearly a hundred different kinds have been discriminated, all produced by different—but closely allied—species of gall wasps.

Of like import is the fact, that no one has yet succeeded in producing galls experimentally, although attempts of this kind have not been lacking.

Another indication pointing in the same direction comes from Adler's interesting discovery, that galls produced by the same insect, in the alternating phases of its heterogenesis, are markedly different : thus, the common currant gall of the male flower of the oak, is the product of one phase (unisexual) of the existence of a gall-producing insect, which in another phase (bisexual) causes the red spangle gall of the under surface of the oak leaf.

It seems to follow from these considerations, that the stimulus in question must be some specific secretion of the larvæ themselves ; and Beyerinck considers that the salivary secretion is the one specially indicated, the active principle perhaps being some special fermentative or allied bio-chemical process, not as yet discriminated. However this may be, it is evident that very slight differences in the nature of the causative stimulus, determine widely different morphological results in the produced gall; this is specially obvious when, as sometimes happens, several quite different galls, caused by as many different parasites, are formed on the same leaf.

In discussing this subject, Darwin remarks: "As the poisonous secretion of insects belonging to various orders, has the special power of affecting the growth of various plants; as a slight difference in the nature of the poison suffices to produce widely different results; and, lastly, as we know that the chemical compounds secreted by plants are eminently liable to be modified by changed conditions of life, we may believe it possible that the various parts of a plant might be modified through the agency of its own altered secretions. With such facts before us, we need feel no surprise at the appearance of any modification in any organic being."

As exemplifying these remarks, we may profitably recall and contrast the mossy rose-gall, the product of extrinsic parasitic stimulation; and the mossy outgrowths of the calyx of the moss rose, spontaneously arising as the result of unknown intrinsic changes.

The willow galls—caused by a species of *Nematus*—also illustrate the free formation of epidermal trichomes, in response to parasitic irritation.

Another remarkable feature about such galls as we are now concerned with is, that the form assumed by them is beneficial to the parasite rather than to the tree-host; so that it appears as if we must ascribe this effect to a specific stimulus proceeding from the larva, which these formations are obviously adapted to protect, support, and nourish; and it is difficult to escape the conclusion, that this stimulation is in some way connected with the feeding of the larva on the cells of the plant by which it is surrounded. As for the reaction on the part of the tree-host, this may be regarded as an exaggerated and specifically modified outcome of the reparative process. Some remarkable examples of the influence of the stimulus in directing this reaction for the advantage of the parasite, are seen in the case of those galls out of which the parasite is unable to eat its way, when the time for escape has come; for such galls then dehisce, as many fruits do, and so allow the parasite to escape.

In this connexion, however, it should be noted that among the immense number of galls, there are some in which host and parasite live together in a manner that is mutually beneficial (symbiosis); while, in others, the joint existence is very harmful or even fatal to the plant-host.

As an example of the former condition, the remarkable growths occasioned by parasitic ants, in the so-called "ant plants" (*Myrmecodia* etc.), may be cited; which Beccari and others consider to be indispensable for the healthy development of such plants—the latter protecting the ants, which in their turn protect the plant.

In like manner the galls formed on the roots of leguminous plants, owing to the agency of parasitic fungi, contribute to the well-being of the plant, by elaborating and storing nutritive materials for its use.

In these cases, we have evidence that plants subjected to certain stimuli of vital origin respond thereto, not merely by local hypertrophy, but also by profound alterations in their morphological and physiological dispositions, which ordinary mechanical stimuli are unable to elicit.

The earliest changes in gall-formation consist in active growth and proliferation of the merismatic cells—" blastem "—immediately surrounding the parasitic embryo; these cells from the first respect the included larva, for which in the course of their subsequent development a free cavity is formed—the so-called larval chamber; and they subsequently undergo developmental differentiation, much after the manner proper to the normal ontogeny of the affected part.

It is a noteworthy fact that some galls, like abnormally evolving adventitious buds, may be used for purposes of propagation.

Gall-producing parasites are exceedingly numerous and of many diverse kinds, both animal and vegetable forms being represented; but the commoner and more conspicuous galls are generally caused by insecta —most orders of this class comprising some gall-producing representatives, of which *Cynipidæ* and *Acari* are among the commonest; fungi are also responsible for many—*e.g.*, the "apple canker," due to *Nectria ditissima*; and, besides these, various protophyta and protozoa, such as the *Plasmodiophora brassicæ*, which cause the tumour-like swellings on the roots of cabbages etc.

## CHAPTER VII

# THE GENESIS OF MALIGNANT TUMOURS

### Historical Review.

THE ancients of the classical period divided tumours into three great classes: *Tumores secundum naturam, supra naturam, præter naturam.* Physiological enlargements were included in the first; the second comprised swellings due to the displacements of natural parts; while the third embraced all other swellings—a miscellaneous assemblage, comprising all that we now include under the term "tumour," and many other conditions besides.

By Galen [1] and his followers the tumours *præter naturam* were believed to result from the accumulation of one or other of the four humours, each of which generated its corresponding kind of tumour. Of these humoral tumours, those of the group called "scirrhous"—which embraced cancer, and nearly corresponded with that we now understand by the word "tumour"—were believed to arise from the accumulation of atrabile (*Cancer ab atrabile*).

After the long centuries of ignorance, stagnation and superstition, that followed the overthrow of the Roman Empire and classical learning, by swarms of barbarian warriors, the humoral theory at length emerged from the wreck not appreciably altered.[2]

Indeed, it was not until the discovery of the circulation of the blood, early in the seventeenth century (Harvey, Malpighi, Leeuwenhoek, and others), that this doctrine was overturned.

In place of the humours, the blood was now regarded as the true source of the disease.

Early in the eighteenth century the Cartesians, with Boerhaave at their head (*Morbus est vita præter naturam*), ascribed the origin of tumours to the newly discovered lymph—a derivative of the blood: cancer they regarded as the outcome of vitiated, depraved, or degenerated lymph.

Doctrines of this kind continued to hold sway, until the time of Bichat —at the end of the eighteenth century.

With the advent of the illustrious founder of biology, we begin to discern the first rudiments of modern conceptions emerging from the ancient chaos. The philosophical insight of Bichat enabled him—

[1] "De tumoribus præter naturam."

[2] As a historian of medicine has remarked: "Greek medicine of the fifth century B.C. seems to be almost of yesterday; whereas, English medicine of the twelfth century of our era, is as alien and grotesque to our thought as the demonology of the Chaldeans."

without the aid of the microscope and relying only on gross appearances—to decompose the organism into its elementary tissues and organic systems. "Every tissue," said Bichat, "has its own diseases."

This was a great advance on previous ideas; and it is on this basis that the modern anatomico-pathological study of tumours rests, which the labours of Laënnec, Andral, Louis, Bayle and Cruveilhier in the same direction subsequently strengthened and extended.

Thus Bichat anticipated and prepared the way for the cell theory—the culminating point of modern biological progress—although due acknowledgment of this his great achievement has, I think, never before been accorded to him by English, American, or German pathologists.

At this juncture, early in the nineteenth century, the current of thought was suddenly interrupted and changed, by the appearance on the scene of the impetuous Broussais.[1] His doctrine was that all tumours, including cancers, were but forms of chronic inflammation, consequent on organic irritation. The extreme simplicity, comprehensiveness, and positiveness of this crude generalization—suddenly sprung on a scientific world, hesitating between the old humoral doctrines and the nascent anatomico-pathological tentatives—captivated every one; and the Broussaisian system, in an incredibly short time, became supreme.

But its supremacy was short-lived. What more than anything else contributed to its downfall, was the application of the microscope to the study of living things. To this instrument and its revelations, we are indebted for the two great doctrines of modern medical science—the cell theory and the germ theory. The far-reaching importance of the revolution thus effected is, even now, by no means duly appreciated. It might be thought that the history of the invention of an instrument, which has done so much to enlarge the field of knowledge as the microscope, would be a theme for every one; but, as a matter of fact, the discovery is shrouded in obscurity. It is believed that the earliest compound microscope was made by the Janssens—father and son—spectacle-makers of Middelburg in Holland, near the end of the sixteenth century. One of their instruments was exhibited in London—by Drebbel of Alkmaar—early in the seventeenth century (1617). Unfortunately it was imposible to see clearly with this instrument, when high magnifying powers were used, owing to the disturbing influences of chromatic and spherical aberration; hence the compound microscope was at first merely a scientific toy. It took more than two centuries to overcome these defects. At length, early in the nineteenth century—thanks to the skill of Selligues, Chevalier, Tully, Amici, Lister, and others—these difficulties were surmounted. In 1830, a real serviceable compound microscope was at last produced; and with its aid naturalists, shortly afterwards, began to explore the minute structure of organic forms, as Newton had long before predicted. Thus the science of histology was born, which subsequent improvements in optical appliances and a better technique, have advanced to its present remarkable state of perfection.

With this new aid the cellular structure of organized beings was ere long discovered. For the famous cell theory—which must be ranked

[1] "Traité des Phlegmasies chroniques," 1808, etc.

among the most important steps by which the science of biology has ever been advanced—we are indebted to the vegetable morphologist Schleiden; and shortly afterwards Schwann demonstrated the applicability of his generalizations to the animal world (1838). In the very same year the publication of J. Müller's important work on the origin of tumours,[1] established the cellular nature of cancer and other neoplasms. Modern conceptions as to the pathogenesis of tumours date from this period.

Müller believed that the constituent cells of tumours were derived from a formative fluid, exuded from the blood (*blastema*); which was nothing but the coagulable lymph of Hunter, under another name. He ascribed the origin of cancer and other neoplasms, and their variations *inter se*, to aberrations of the force inherent in this primordial substance, causing the resulting cells to deviate from their usual evolution. Müller also strongly insisted on the correspondence between the development from the embryo, and the pathological neoplastic process: "It is one and the same power which, being maintained continuously from the germ to the latest period of life, determines all organic formation."

The pathological cells, he maintained, differed from the physiological cells only in respect to the degree of evolution ultimately attained. The division of neoplasms into two great classes, according as their structure resembled the normal tissues (homologous), or differed from them (heterologous), Müller completely rejected. "It is evident," he says, "that no division of pathological structures into homologous and heterologous can be established. Such a classification is formed without any knowledge of the structure of morbid growths, and is founded on blind gratuitous hypothesis. The most innocent growths do not differ in their minute elements, nor in their origin, from the most malignant ones."

The establishment of the cell theory gave an immense impetus to pathological histology, and a vast mass of new data soon accumulated. Virchow,[2] some twenty years later, pounced upon these; and, with wonderful insight, skill, and energy, elaborated them, together with independent observations, into a kind of new cell theory, which still prevails. Virchow's influence on modern conceptions has been so great, that it will be of interest to trace the genetic relationship of his ideas with those of his predecessors. It may be said that he adopted the cell theory in its entirety, as laid down by Müller, with the single important exception, that he completely exorcised the blastemal origin of cells. It was just this omission that chiefly constituted the novelty of his system. Instead of a hypothetical blastema, he substituted the famous formula "*Omnis cellula è cellulâ*" = "Where a cell arises there a cell must have previously existed, just as an animal can spring only from an animal, and a plant from a plant." Thus the doctrine of continuous cellular development, that had been established by Remak for the normal tissues, became the basis of Virchow's neoplastic pathogeny.

Another important respect in which Virchow's cellular pathology of tumours differs from that of his predecessors, is in the addition to it of

[1] "Ueber den feineren Bau und Formen der krankhaften Geschwülste," 1838.
[2] "Cellular Pathologie," 1859.

the whilom extinct Broussaisian doctrine of irritation and chronic inflammation.[1] Nowhere in Virchow's works have I met with any attempt to explain the compatibility of this irritation hypothesis, with the doctrine he also adopted, of the correspondence between the embryonic and neoplastic developmental processes. In my opinion, these views are absolutely incompatible; and this incompatibility constitutes a serious flaw in Virchow's neoplastic pathogeny. I believe that tumour formation is the outcome of formative hyperplasia (*e.g.*, growth), and not of inflammation. By most pathologists these two fundamentally distinct processes are confused together, and treated as being one and the same; whereas, my belief is, that they are in every respect different and distinct. Inflammation is the outcome of extrinsic causes; whereas, the causes which determine neoplastic hyperplasia are, as I shall show in the sequel, mainly intrinsic. Moreover, the two processes are morphologically distinct. In short, the morphological and biological characters of tumours show, that neoplastic pathogenesis is something quite different and distinct from all inflammatory processes. As Billroth has remarked,[2] if we once allowed the principle of the correspondence between the embryonic and neoplastic processes to be lost sight of, we should necessarily fall back "into the old chaos of parasites and pseudo-plasms," which is exactly what we are now experiencing.

Of late, owing to a variety of causes, Virchow's doctrines have undoubtedly lost ground. For this lapse, Virchow himself is to a large extent responsible. As is well known, his dogmatical and didactic mind entertained deeply rooted aversion for all kinds of theories and hypotheses. It was this lack of scientific imagination, that caused him to go out of his way, in a really extraordinary manner, to prevent his followers from assimilating the new facts and principles brought to light by modern biological progress, in connexion with the doctrine of evolution. Another consideration that tended to confirm him in this opposition, was the fact that in the domain of neoplastic pathology, wherein his ideas concentred, evolutional conceptions seemed to have but little application; for most pathological neoplastic phenomena are the outcome of the failure or undoing of evolution. Hence, while the rest of biology has been revolutionized, the cellular pathology has remained stationary.

So far as the pathology of neoplasms is concerned, in my work on "The Principles of Cancer and Tumour Formation" (1888), I endeavoured to repair Virchow's error, by laying the foundation of a modified cellular pathology in harmony with modern biology; and—although this work has hitherto received no recognition from contemporary pathologists, preoccupied with various kinds of will-o'-the-wisps—I confidently look forward to the time when the conceptions there embodied will be generally accepted, as furnishing the only really scientific basis for explaining the phenomena of pathological neoplasia; which, as I have there set forth, is at the bottom essentially a biological problem. Hence, nothing will be more conducive to this end, than the wider spread of biological knowledge and conceptions among modern pathologists; who are, even now, for the

[1] "Die krankhaften Geschwülste," Bd. i., 1863 (third lecture).
[2] "Surgical Pathology," 1879, p. 600.

most part, very deficient in this respect, as so many recent publications testify.

Another circumstance that has tended to weaken Virchow's authority, is the large measure of success accorded to a modification of the cellular theory propounded by Cohnheim,[1] according to which tumours are derived from displaced fragments of the germinal matrix, sequestered during the earliest period of embryonic life.

In this, its original primitive form, the theory was only capable of very limited application ; but, as subsequently modified, so as to include sequestrations of the various tissues and organs arising at later periods of embryonic and post-embryonic life (" rests "), it embraces a very large number of facts relating to tumour genesis.

Moreover, in this way attention was directed to the frequent association of tumour formation with various kinds of developmental irregularity—a very important indication.

That a considerable proportion of malignant and non-malignant tumours actually do arise in this connexion, I have convinced myself.

There are, in fact, good reasons for believing—as I shall presently show—that tumours are specially apt to arise wherever cells, still capable of growth and development, are present ; and, that they are most prone to originate, where such cells most abound.

**The Present Controversy.**

But what more than any other recent occurrence, has undermined the authority of the cellular neoplastic pathogeny is the widespread belief, that tumours will ultimately turn out to be of microbic origin. In short, it is evident, that out of the confusion of a transitional period, but two conceptions as to the origin of tumours have emerged—the one based on the cell theory, and the other on the microbe theory ; and henceforth the struggle must be between these two. Briefly stated, the question now is : Do cancers and other tumours arise through modification of the formative process ; or, are they the outcome of the inflammatory process, owing to the intrusion of microbes, or other irritants *ab extra ?* In other words : Are they essentially of *intrinsic* or *extrinsic* origin ?

Those who incline to the former alternative, look to the biological properties of the cells of the affected part, for the key of the problem : whereas, the other side, refer all the essential phenomena of the disease to the activity of parasitic microbes, or other external irritants.

When the issues are thus plainly stated, the great importance of choosing a working hypothesis at once becomes apparent ; for, of the two alternatives, only one can be true. My own belief is, that tumours arise mainly from the abnormal play of forces generated within the body ; and it is to this aspect of the question that I now propose to direct attention.

[1] " Vorlesungen über allgemeine Pathologie," 1877.

### The General Theory of Intrinsic Pathogenesis.

It has hitherto been customary, as I have previously intimated, to regard tumour formation as an isolated pathological entity, having no connexion with other biological processes. This seems to me to be a fundamental mistake; for, the first step towards a rational interpretation of tumour genesis from the biological standpoint, must necessarily be the discovery of its true affinity. Now, it is in morphological variation in general, as I have previously indicated, that this affinity is to be found. Indeed, what is variation but a novel kind of cell multiplication? And what is tumour formation but a special variety of this novelty? And is not every variation, as Virchow suggested, essentially pathological? The answer to all these queries—as we now see—is, as implied. Variation, mutation, and tumour formation, these are but different manifestations of one and the same process.

In the preceding chapter, I have traced the connexion between these kindred manifestations, as it occurs in vegetable organisms; where tumour formation was shown to be an outcome of abnormal gemmation, which is a form of agamogenesis.

In human and animal organisms, the biological significance of tumour formation is precisely the same, as I have shown at some length in my book on "The Principles of Cancer and Tumour Formation."

In that work I have adduced reasons for believing, that there is no fundamental, specific distinction between such apparently varied biological processes, as the various modes of reproduction—gamogenetic and agamogenetic, the processes of repair, maintenance and new formation of tissues, the reproduction of lost parts, and the various morphological variations—including bud, cancer and tumour formations.

All of these apparently so different phenomena, are there shown to be merely protean modifications of one common process, which underlies and is the cause of them all—to wit, cell growth and proliferation. The particular outcome of the process in any given case, is shown to be due to the influence of the conditions of nutrition—understanding by this term the whole of the material changes wrought in the organism through its relations with the surrounding outer world. This being so, it is easy to understand how, under favourable conditions, certain cells may take on independent action, growing and multiplying, without regard to the requirements of adjacent tissues, and of the organism as a whole. Thus the various pathological new formations arise. From the biological standpoint, then, tumour formation must be regarded as a phenomenon of the same order as reproduction in general; that is to say, as a special form of overgrowth of the individual.

The nearest congeners in the biological domain to the tumours of human and animal pathology, must be sought in the suddenly occurring, non-adaptive new formations, known to biologists as "sports," "bud variations," "spontaneous variations," "discontinuous variations," etc., all of which abrupt transformations may be conveniently comprised under the term "mutation," as suggested by De Vries.[1]

[1] Although the term "mutation" belongs to De Vries, the mutation theory was founded by Bateson ("Variation," 1894).

Moreover, all of these kindred processes may be regarded as being dominated by a common ætiological factor, since, in ultimate analysis, they may be ascribed to the cumulative effects of changed conditions of existence—of which, in the case of animals, the most important items probably are excess of food, changed environment, and want of proper exercise.

Another question of fundamental importance remains to be considered, before we can proceed to the study of the process of tumour genesis; and this is the question as to the relations of the somatic and germ cells to one another, and to the organism as a whole.

After very thorough study of the chief types of reproduction throughout the organic world, Herbert Spencer[1] concluded that we are justified in assuming, that every component cell of the multicellular organisms has the inherent power, under favourable conditions, of developing into the form of the parental organism: so that each cell may be regarded as potentially the whole organism. According to this conception—with which Darwin and Haeckel were in agreement—the reproductive properties manifested by somatic and germ cells are the same in kind, and differ only in degree.

This doctrine has been strenuously attacked by Weismann and his followers, who have founded their theory of heredity by continuity of the germ-plasm, on the assumption that the reproductive properties of somatic and germ-cells are specifically different: at least, this was the initial conception; but, when it was subsequently demonstrated that in many plants and animals (*e.g.*, mosses, hydra etc.), almost any cell sufficed for the reproduction of the entire organism, this difficulty was met by the supplementary hypothesis of "accessory" germ-plasm ("idioplasm"), which in such cases was supposed to have become diffused throughout the soma protoplasm.

But such a conception dispenses with the necessity for the original hypothesis; for, if all or most of the soma protoplasm can manifest this reproductive capacity, it is surely much more likely that this property is inherent in its structure, rather than that it is due to the intrusion of hypothetical "germ-plasm" *ab extra*.

Thus, in my opinion, the validity of Spencer's conception remains unimpaired. As I have fully set forth the very convincing evidence supporting this conclusion, in my work on "The Principles of Cancer and Tumour Formation,"[2] there is no need for me to enter into detailed restatement of the same here. For our present purpose, it will suffice if I recall, in the briefest manner possible, some of its chief features. From this standpoint, what are we to think of the fact that a single scale from the leaf, stem, or root of a plant, suffices for the reproduction of the whole organism (mosses, begonia etc.); or that nearly as small a particle of the Hydra and other animals, is able to reproduce the whole organism? Does not the whole history of adventitious gemmation in plants, as detailed in the preceding chapter, testify against fundamental difference between somatic and germ cells? Is it not the same with gemmation in

[1] "Principles of Biology," 1884.
[2] Chap. xi.

animals, with asexual reproduction, with metagenesis, and with parthenogenesis? Do not the phenomena of repair, and the reproduction of lost parts, testify to the same effect? I say that they do.

The very remarkable manner in which the majority of British biologists were at once captured by Weismann's fascinating intellectual divagation, is one of the features of the history of the scientific life of the period: it is likely to rank with the celebrated heresy of Liebig, as to the non-microbic nature of fermentation, which retarded the advent of the microbe theory for such a lengthy period; and with the vagaries of Cuvier, which caused his curious hypothesis as to the origin of species, to be preferred to the more truthful conceptions of Lamarck, and so retarded the progress of modern biology for more than half a century. As the veteran R. Owen,[1] so well remarked, when these biological speculations first began to swarm: "If science is to retain its strength, it must keep in touch with the solid ground of observation. In reading some of the biological literature of the day, I sometimes rub my eyes, and wonder whether I am not dreaming of the good old days of the *Natur-philosophie*." To be quite frank, I regard the great body of scientific truth relating to growth, reproduction, variation, heredity, and allied biological problems, as being on the whole more fully enshrined in the works of Spencer and his great lieutenants Darwin and Haeckel, than in any other publications; and it is mainly on this basis that I have built up my doctrine of tumour formation.

In the genesis of tumours, as in the genesis of other organic structures, I believe we must take into consideration two factors—the *cells* whence they originate and the *force* that regulates the cellular activities.

With regard to the cells, although each is largely dependent upon others, yet at the same time each manifests a certain independence or autonomy. In the special changes underlying pathological new formations, the autonomy of the cells plays an important part. It is quite certain that somatic cells are possessed of far greater reproductive power, than they ever ordinarily manifest. Evidence of this is seen in the processes of repair and regeneration, in the changes that take place at puberty and in connexion with pregnancy—when the breasts and uterus undergo such remarkable metamorphoses—in the phenomena of compensatory hypertrophy, and in a variety of other processes. Strange to relate, this wonderful reproductive capacity, which enables us to understand how a single cell may originate even the largest tumour extant, has received but scant attention from pathologists in explaining the neoplastic process. That the reproductive activity actually manifested by somatic cells usually falls so far short of their potentiality, is believed by Spencer to be due to the restraining and modifying influence exerted by the whole organism on their protoplasm; which is thus compelled to the performance of comparatively subordinate, modified functions. In the performance of these special duties, most of the protoplasm is metamorphosed and used up. Hence, in proportion as the cells are highly specialized, their reproductive function is either greatly reduced or altogether lost. But, in the higher organisms, certain cells never attain a high degree of development; they remain in a lowly organized

[1] Owen's "Life," vol. ii., p. 330.

condition, and serve—according as they are more or less unspecialized—either as germs for reproducing the entire individual, or for forming and maintaining the various tissues and organs. Cells of this kind abound in all parts growing and capable of growth. These are the sources whence cancer and tumour germs are derived.

In the ordinary course of organic evolution, the processes of cell growth and multiplication go on, until the amount of structure proper to the organism has been produced; then they are restricted within certain limits. In the healthy organism, this state of balanced equilibrium is maintained throughout the whole life of the individual. Herein is evidence of a force regulating the growth and development of the tissues and organs in relation to each other, and to the organism as a whole. In order to account for this, it may be assumed that, by a kind of selective assimilation, the molecules of each part have the power of moulding the adjacent nutritive materials into molecules, after their own kind. "Like units," says Spencer, "tend to segregate, and the pre-existence of a mass of certain units produces, probably by polar attraction, a tendency for diffused units of the same kind to aggregate with this mass, rather than elsewhere." In the case of the reproduction of a lost part, it must be assumed that the organism, as a whole, exercises some such power over the newly forming part, so as to make it a repetition of its predecessor. "If a leg is reproduced where there was a leg, and a tail where there was a tail, we have no alternative but to conclude, that the aggregate forces of the body control the formative processes going on in each part."[1]

In like manner the mimicry—morphological and physiological—by tumours, of the parts whence they originate, which is always so noticeable, may be explained.

So long as the growing cells are subject to this normal restraining influence—which has nothing to do with the nerves and bloodvessels, themselves integrated structures—they develop in a regular and orderly manner, in accordance with the specific hereditary tendency of the whole. But when under pathological conditions, this restraining influence is modified or withdrawn, then their potential reproductive activity may become actual. Cells thus emancipated grow and multiply more rapidly than their congeners. This rejuvenescence is the essence of the neoplastic process. Hyperplasia and not inflammation is the starting-point of every neoplasm. Redundant agamic cell generations are thus interpolated in the developmental series, without the concurrence of the conditions necessary for their potentialities attaining a physiological terminus.

The developmental outcome of cells thus abnormally set free, depends chiefly upon the degree of emancipation attained. In plants and the lower animals, such cells tend to form new individuals by agamogenesis; but, in the higher animals, the emancipation is never so complete, and their cells are always more or less differentiated; hence, in these organisms, instead of new individuals, only such structural modifications as tumours

[1] This conception seems to me to have far more scientific validity than the alternative hypothesis of "tissue tension," etc., adopted by some German pathologists (Weigert, Ribbert, etc.).

are produced. Under these circumstances, wherever there is a sufficient supply of nutritive materials, capable of being utilized for growth by the cells of the part, there a neoplasm will arise ; that is to say, the abnormally emancipated cells will there grow and multiply more or less independently, regardless to the requirements of the adjacent tissues and of the organism as a whole. In other words, a new centre of development has arisen. Thus the process by which cancers and other neoplasms arise may be regarded as a kind of abnormal gemmation, the tumour being the result of the modified superinduced repetition of the developmental process ; and its qualities, the result of the degree of emancipation of its elements. In the case of malignant tumours, cell potentialities of the highest order have been awakened ; hence the excessive proliferative activity of their constituent cells and their other peculiar features, which together constitute malignancy.

If we regard the cells combining to form the higher animals as autonomous beings,[1] possessed of morphological and physiological independence, we shall then see—although there is no such thing as true alternation of generations in the ontogeny of such animals [2]—that, nevertheless, as Haeckel has pointed out, a very complex alternation of the constituent cells does take place, which has a resemblance to it. The developmental cycle commences with the union of the male and female reproductive cells, whence the cytula or fertilized germ results ; which, by agamic multiplication, originates the mass of similar cells called the morula. These differentiate into the various cells of the blastodermic layers. By further agamic multiplication, the cells of these layers originate the very many generations of variously modified cells, whence the different tissues and organs arise. All of these polymorphic cell generations multiply agamically. Eventually, however, two of them differentiate sexually, forming the ova and sperm cells. By the union of these, in the act of sexual reproduction, the developmental cycle is completed. The reversion of the cells has led them back to their original starting-point.

The only difference between this process and true alternation of generation lies in the fact that, in the former, the products of agamogenesis remain in close contact with one another to form a multicellular organism ; whereas, in the latter, the agamic products (persons), which represent the different generations, are separated and free. But, the conditions prevailing in *Siphonophora*, show that this distinction is not of fundamental importance ; for, in these creatures, the same persons—widely differentiated by division of labour—remain united into one stock, that in the other hydro-medusæ lead separate and independent lives. Thus, when the phenomena of gemmation and pathological neoplasia are examined in this light, it is obvious that the essential thing in both cases, is the interpolation in the developmental series of additional agamic cell

[1] "All the facts at our command indicate that the tissue-cells possess the same morphological organization as the egg-cell or the protozoön ; and the same fundamental physiological properties as well," says E. B. Wilson, the ablest exponent of cellular biology for English-speaking peoples (1903).

[2] According to Dr. Beard, even in mammalia true alternation of generations does occur, the asexual larva being represented by the chorion ; but, at present, this speculation is no more than an unproved hypothesis. The conception, however, is of interest ; and, on general *a priori* grounds, there is much in its favour.

generations, owing to the excess of nutrition in these situations. From this standpoint, tumour formation appears as a reversion from dominant gamogenesis, to a form of agamogenesis.

It follows from the foregoing, that the genesis of cancer and other tumours, is a phenomenon of the same order as discontinuous growth in general.

Just as cells embedded in the stroma of an ovarium, become ova by excessive growth, at the expense of adjacent nutritive materials, which they divert from other cells; so we may infer that those cells which originate tumours, become different from their congeners in a similar way.

### Tumour Formation and Developmental Irregularity, with Special Reference to the Rôle of "Rests" in the Origin of Tumours.

I have previously referred to tumour formation, as being the outcome of a futile attempt of certain cells to repeat agamically a greater or less portion of the ontogenesis.

In order to elucidate the various types of tumours and their diverse qualities from this standpoint, it is necessary to pay particular attention to the germs whence they originate; and to the time at which the process starts.

Cohnheim, who was the first to study this question systematically, thought that the germs of all tumours were fragments of the fertilized germinal matrix, sequestrated during the earliest period of embryonic life. His tumour germs were therefore blastogenic.[1]

The researches of embryologists and teratologists, have shown that tumour germs of this kind may really exist.

Having destroyed one of the first two cells resulting from the initial division of the impregnated frog's egg, Roux, Hertwig, Chabry and Morgan, found that the other cell, nevertheless, developed into a whole embryo of half the normal size; by shaking the germs of various animals and so separating the blastomeres, Driesch, Wilson and others found, that each detached blastomere likewise developed into a whole embryo of half-size. It has been found that blastomeres isolated at even the four-, eight-, or sixteen-cell stages, may sometimes develop into small but complete embryos. At later stages, however, detached cells are never capable of undergoing such complete developmental exegesis; for, as Driesch and others have shown, when pieces are cut from the evolving organism after gastrulation, they do not develop into perfect larvæ, but only into various defective or monstrous forms. These experiments indicate that the power of a single cell to reproduce the entire organism is, in the highest animals, limited to the earliest stages of cleavage; for it is only these cells that contain all the elements requisite for complete developmental exegesis.

In the course of his various experiments, Roux often noticed in frog embryos with closed medullary canal, isolated blastomeres, belonging to a

[1] Even before Cohnheim's time, Lücke and others had advocated a similar origin for teratomata.

much earlier developmental stage;[1] and these he thought might become tumour germs. Beard has met with a similar condition in studying the embryology of *Raja batis;* while Barfurth, experimenting as to the regeneration of the germinal layers, found when these were punctured in the gastrula stage, so that cells were displaced and involuted, that these heterotopic elements nevertheless continued their growth, in such a manner as suggested the probability of their eventually becoming tumour germs.

Wilson, Roux, and others, by shaking and various other mechanical devices tending to separate the blastomeres, found that in this way homologous twins and various grades of double mounters were frequently produced.

By the implantation of blastoderms of fowl's eggs, embryos, and fragments of the same, into the subcutaneous tissues of chicks, Féré[2] claims to have succeeded in producing teratomatous tumours artificially; and the remarkable result obtained by Nichols,[3] by implanting the entire fœtus into the subcutaneous tissue of the mother, whence a tumour—very like a teratoid—was produced, supports Féré's claims.

It follows from consideration of the foregoing facts, that the only kind of tumours likely to arise from Cohnheim's blastogenic germs, are those in which the whole ontogenetical cycle is structurally represented; that is to say, the embryomata or teratoid tumours, which may be regarded as the very imperfect twin brothers or sisters of the *porteur*. This kind of neoplasm is the type of tumour formation *in excelsis*. Such tumours might with equal propriety be classed with the double monsters by inclusion, for they are identical with those formations described by teratologists as *fœtus in fœtu*. So far then as these tumours are concerned, tumour genesis is seen to be akin to teratogenesis—developmental irregularity being the factor common to both.

It seems not unreasonable to regard the process by which such results are attained, as being a kind of reproduction by gemmation; here, as in the lowest organisms, when the growth of the fertilized germ exceeds a certain amount, it tends to the formation of one or more new individuals, rather than to further enlargement of the original one.

Cohnheim thought that his blastogenic tumour germs might begin their growth into tumours immediately after sequestration, or at any subsequent period of the ontogenesis; or that they might lie dormant in the tissues, without ever undergoing any further change. The life-history of teratoid tumours seems to warrant this suggestion; which is also in accordance with appearances observed by embryologists.

It not unfrequently happens that malignant neoplastic changes—epitheliomatous and sarcomatous—supervene in connexion with these teratoid formations; and changes of this kind are no doubt of commoner occurrence in them, than in the corresponding parts of normally constituted beings. This is only what might be expected *a priori*, considering

[1] R. Owen was one of the first biologists who specially called attention to aberrant cells of this kind: "which may remain unchanged and become included in the body of the embryo" ("Parthenogenesis," 1849).

[2] *C. R. Soc. de Biologie*, 1905; also *Arch. d'Anat. Micros.*, 1897-1898.

[3] Third Report Croft Cancer Committee of Harvard Medical School, 1905, p. 120.

the manifold imperfections in their development, and especially their undue richness in lowly organized cells still capable of growth and development; and, therefore, endowed with a high degree of proliferative potentiality.

From the genetical standpoint, tumours may with propriety be divided into two classes: (*a*) the teratoid (blastogenic); and (*b*) the histioid (somatogenic).

It is to the genesis of the latter group of tumours, that we now have to direct our attention.

As I have previously remarked, after gastrulation and the differentiation of the germinal layers, no cells are ever formed in the higher animals, like those of the morula, whence a complete new being may be formed. Cells subsequently arising can only develop certain tissue structures, viz., those which are normally derived from the germinal layer whence they originate; thus, derivatives of the epiblast always remain within this type, and never originate mesoblastic structures, and *vice versâ*. In the development of tumours, the same law is observed: there are among these formations no transitions from one tissue-type to another. It is necessary to insist on this, because some modern pathologists still uphold X? the ancient doctrine of metaplasia—countenanced by Virchow—according to which, the connective tissue is regarded as an indifferent matrix, whence any tissue may arise. This doctrine ignores the specificity of the tissue elements, which embryology has revealed; and it must therefore be rejected.

From the foregoing considerations, it follows that the physiological prototype of a histioid tumour, must be something less than an entire individual: their prototypes are, in fact, to be found in the various organs and tissues of the body, as they are formed after the differentiation of the germinal layers, whether in pre- or post-natal life. Thus, the precise period of time at which histioid tumours may originate is subject to wide variation, and this entails in the resulting neoplasms corresponding diversities; for, as ontogenesis proceeds, there is concomitant differentiation, first of the cytoplasm of the cells and subsequently of their nuclei, whereby progressive loss of reproductive capacity is entailed, so that—in certain cells—it may eventually be impossible to elicit any proliferative activity by ordinary stimuli.

Hence the portion of the ontogenetical cycle mimicked by histioid tumours, must necessarily in all cases be less than that compassed by their teratoid congeners; but, between these extremes, all grades of intermediate variations occur.

In the ordinary course of organic evolution, the growth and development of the cells proceeds in a regular and ordinary manner, in accordance with the specific hereditary tendency of the whole. But the process once started, does not cease on account of irregularity, or because it is taking a wrong direction. Hence cells may arise at a place where they have no business; or at a time when they ought not to be produced; or to an extent that is at variance with the normal formation of the organism.

In the earliest stages of ontogenesis, as we have seen, teratoid tumours and double monsters are among the consequences of these developmental irregularities ; and, at later periods, the various histioid tumours, in like manner result.

The rudiment of the embryo begins to appear very soon after gastrulation ; and by the end of the third month of intra-uterine life, the general form of the body and its members is well defined. The germs of the more complicated forms of " mixed tumour," dermoids, etc., are probably caused by developmental disturbances affecting the embryo, during the earlier part of this period. As the life-history of these formations shows, malignant neoplastic disease may originate from them at any stage of their exegesis ; and there are good reasons for believing that they are more prone to originate such changes, than are their normally evolved tissue prototypes.

Later developmental disturbances, which may even extend to the post-natal period, cause less extensive reactions ; confined, for instance, to the rudiments of particular organs, parts or to single tissues etc.

Underlying the above remarks is the assumption, that the germs of histioid tumours arise, like those of teratoid tumours, by sequestration of fragments of the matrix of the evolving organs, tissues etc., at different stages of their exegesis, owing to various forms of more or less local developmental irregularity.

For the moment, let us assume that all histioid tumours arise from germs of this kind, which we will call " rests." Of these structures, as of their blastogenic congeners, it may be predicated from study of the life-history of histioid tumours ; that they may begin to grow into tumours forthwith, or at any subsequent period of the developmental stage, or that they may remain permanently latent in the tissues.

In order to further elucidate the rôle of " rests " in the origin of histioid tumours, it will be well to review the evidence bearing on this subject, that has accumulated of late ; especially as, in the publications of British pathologists, this subject has hitherto been very inadequately treated.

When this theory of tumour genesis was first announced, very few facts could be adduced in support of it. No one then believed in the possibility of such an amount of developmental irregularity as it presupposed. The light of modern science has, however, effectually dissipated this misconception ; and our eyes have been opened to the hidden defects of normality. Sequestrated fragments of the various tissues and organs have now been found to exist, in every part of the body that has been specially examined for them. In short, it is evident that, in the course of ontogeny, innumerable fragments of the evolving tissues and organs are thrown off ; which, as development proceeds, become embedded in the tissues—where, as a rule, they remain quiescent. Thus, during the last thirty years, pathologists have added a new chapter to human morphology ; of which, however, the anatomists—as yet—seem hardly to be aware. It is to belated structures of this kind, that the term " rests " is applied. My conception of the significance of this term differs somewhat from Cohnheim's. He thought that " rests " consisted solely of germ elements ; which, after sequestration, lay dormant in the body as embryonic rudiments. As previously mentioned, " rests " of this kind probably exist, and from them blastogenic tumours arise ; but, the "rests" with which histology has made us acquainted, always present indications of having undergone more or less developmental exegesis, along the lines proper to the parental tissue.

Long before Cohnheim's time, the proneness of certain congenital defects to originate malignant tumours had been recognized by pathologists, especially by Paget, Pemberton, and Virchow. That nævi are particularly apt to develop malignant disease, is a very ancient discovery ; it was, for instance, well known and commented on by Récamier, Walther and others, at the beginning of the nineteenth century. Even as far back as 1853, referring to the proneness of melanomata to arise from pigmented moles, Paget[1] said : "It seems a striking illustration of the weakness in resisting disease, which belongs to parts congenitally abnormal." In another passage he adds : "This peculiarity may make us suspect that there may be other, though invisible, defects of first formation in our organs, which may render them, or even small portions of them, peculiarly apt for the seats of malignant and other specific diseases."

In 1858, Pemberton[2] pointed out that of thirty-four cutaneous melanomata, studied by him, no less than fifteen obviously arose from congenital nævi, moles, warts, or other local blemishes.

About the period 1854-1855, Remak[3] having demonstrated the origin of "cholesteatomata" from detached, invaginated, epidermoidal "rests"; also showed that the occurrence of malignant epithelial tumours, in regions where epithelium is normally non-existent, was the result of heterotopia of pre-natal origin.

Roser,[4] at about the same time, traced the origin of dermoids of the neck to sequestration of epidermoidal elements, in connexion with the closure of the branchial clefts ; while Verneuil[5] demonstrated, in a very conclusive manner, the genetic connexion between scrotal, testicular and other dermoids, and somewhat similar local developmental irregularities.

Subsequently Virchow[6] developed the subject still more fully, showing that sarcomatous tumours of the skin often originated from nævi, moles, soft warts (verrucæ molles), and other congenital anomalies.

Under these circumstances, it seems unreasonable for the admirers of Durante[7] to claim for him the authorship of the "rest" theory of tumours, because he published—a year or two before Cohnheim's "Vorlesungen" appeared—a brochure[8] on : "The Physico-pathological Connexion between Maternal Nævi and the Genesis of some Malignant Tumours." Paget and Virchow never advanced such claims, although they were far more entitled to do so than Durante. The truth is, for

[1] "Surgical Pathology," 1853, vol. ii., p. 490.
[2] "Observations on Pathology, etc., of Cancerous Diseases," part i. (Melanosis), 1854.
[3] "Deutsche Klinik," 1854, p. 160.
[4] "Handb. d. Anat.-chir.," 1854.
[5] "Mém. sur. l'inclusion scrotale et testiculaire," 1855.
[6] "Path. des Tumeurs," 1869, t. ii., p. 218 *et seq.*
[7] Eyre, *British Medical Journal*, 1896, vol. ii., p. 1441.
[8] *Archiv. di Palasciano*, May, 1874.

those acquainted with the works of Paget and Virchow, there was nothing new in Durante's publication. The credit of elaborating the indications furnished by these pioneers, together with his own observations, into a comprehensive theory of tumours, and making the same known to the profession in general, undoubtedly belongs to Cohnheim. This conception seems to have originated in his mind, through careful study of a case of renal myo-sarcoma that came under his observation, in an infant sixteen months old. The left lumbar region was occupied by a large circumscribed tumour, which had destroyed most of the kidney by compression, the remains of this organ—otherwise unaltered—being adherent to it. Within the capsule of the right kidney—at its upper end—there was also a similar rounded tumour, quite distinct from the renal substance. Both tumours were sarcomatous, and comprised in their structure striped muscle elements. It seemed evident to him, that tumours thus circumstanced could only have arisen from heterotopic elements, detached from their normal connexions during early pre-natal life; hence, other facts known to him concurring, he concluded that all tumours thus originated.

### Uterine Tumours and "Rests."

We have now to study a little more closely the genesis of histioid tumours from "rests"; and, as this is far too large a subject to treat here in detail, I must be satisfied with giving a few typical examples. For this purpose, I have selected uterine and mammary tumours, as I have made a special study of these; another reason for so doing being, that tumours of these organs have hitherto received hardly any attention in this connexion.

**Myoma.**—By far the commonest non-malignant tumour to which humanity is prone is the familiar, but little studied, uterine "fibroid," or myoma, whose structure so closely resembles that of the uterine musculature, as to suggest the probability of these tumours being little more than overgrown fragments thereof, which thorough study of the ensemble of the subject emphatically confirms. Moreover, it will be proved that the germs whence these tumours arise are sequestrated during pre-natal life. The great frequency with which uterine myomata are multiple, might of itself lead us to suspect the association of developmental irregularity with the origin of these tumours; while the occurrence of cases in which the whole musculature is replaced by dense masses of small tumours—to which I shall subsequently have to refer more in detail—specially points to this conclusion.

Although the germs whence most myomata arise are of pre-natal origin, it is rare—as in the case of such obviously congenital tumours as teratoids and dermoids—to meet with tumours of this kind during early life: Pick[1] has, however, described two cases of congenital myoma, in each of which the nascent tumour seemed to have caused uterine duplicity, by interfering with the blending of the lower segments of the Müllerian ducts; and, in a case reported by Landau,[2] a myomatous tumour—

[1] *Monats. f. Geb. u. Gyn.*, October, 1897.
[2] *Berlin. klin. Woch.*, No. 8, 1901.

obviously of congenital origin—occupied the place of the cervix uteri, and by compressing the Müllerian ducts in the pre-natal period had caused atresia uteri, there being no canalis cervicalis: this tumour contained numerous epithelial inclusions, which appeared to be Wolffian *residua*.

The fact that uterine myomata often contain various heterotopic inclusions—comprising epithelial, cartilaginous, calcareous, osseous, mucoid, fatty and even rhabdomyomatous elements—points to their pre-natal origin.

Recent researches (Rösger, Kleinwächter, Sobotta etc.) have shown that the development of the uterine musculature, is closely associated with that of its numerous bloodvessels. The nascent utero-vaginal canal, having no proper musculature of its own, is provided with the same through the agency of a matrix of mesoblastic cells, which creep round it with the evolving bloodvessels. Should the development of the latter be arrested, when this process has already made some progress, the outcome might well be just such fragmentation of the musculature, with more or less overgrowth of the fragments, as in the specimens described in the following case records, which seem to be quite unknown to contemporary gynæcologists:—

1. This patient was under the care of Emmet.[1] When first seen by him she was in a very weak and emaciated condition. There was great abdominal distension from the tumour, and she suffered much from pressure symptoms. Strange to say, there was no metrorrhagia. She died of exhaustion soon after Emmet first saw her.

At the necropsy, the tumour was found to consist of the greatly enlarged uterus, converted into a large conglomerate of hundreds of myomatous nodules—none of great size—held together by a thin overlying capsule, through which their inequalities could be seen and felt. On section the mass presented the appearance shown in Fig. 6 (next page). The division was made with difficulty, as many of the tumours were of dense fibrous nature, and others were calcified. The bloodvessels of the part were obliterated to such an extent, that only the peripheral nodules presented any signs of vascularity. Emmet subsequently met with a second case of the same kind.

2. Meadows[2] has described a similar case as follows: "I have seen the uterus completely studded with myomata, both within and without, so that on making a section of the uterine wall, the surface looked like the skin of a person with small-pox; so numerous were the tumours that it was impossible to count them. They varied in size from a millet-seed or less, to that of a small walnut."

3. Cruveilhier[3] has encountered the like condition. In his case the whole musculature was replaced by a multitude of small tumours of this kind, most of which were very minute, the largest being no bigger than a walnut. Many of the tumours were calcified. The affected uterus presented as an irregularly bossed mass, not unlike an ovarian cystoma to look at. Some of the tumours projected externally and others internally, but most of them were embedded in the musculature.

[1] *Gynæcology*, 1880, p. 525. [2] *Gynæcology*.
[3] "Anatomie Pathologique," t. ii., liv. xxiv., p. 5.

Bland-Sutton[1] and Haultain[2] have also met with this condition, which each of them regarded as "unique," being unaware of the very explicit account of this malady in my book on "Uterine Tumours."

Instead of involving the whole organ, multiple myomata are sometimes limited to a special part. In the Hunterian Museum,[3] is a uterus with numerous tumours of this kind, which occupy every part of it, except the cervix and portio, which are free. Rabenau[4] has met with similar tumours limited to the cervix and portio. Stone[5] has described a multinodular tumour of the corpus, which consisted of an immense number of small growths of various shapes.

If we conceive this process, as restricted to a still narrower area—to a

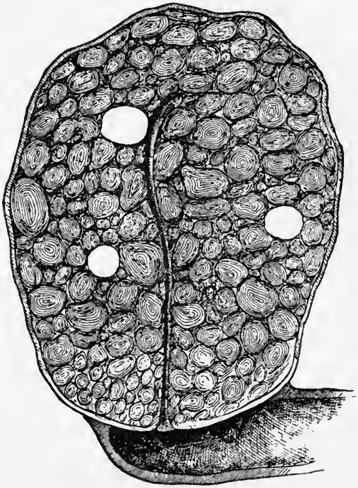

FIG. 6.—MULTIPLE MYOMATA INVOLVING THE WHOLE UTERUS (EMMET).

The white areas represent calcified tumours.

few vascular branches, or even to a single one—it is easy to understand how the germs of ordinary myomata arise. Thus, these cases are of great importance, for enabling us to understand the pathogenesis of myomata.

In some instances, these abnormally evolving myomatous elements are intimately connected with "rests" of Wolffian or Müllerian structures, or even of the uterine mucosa itself. The discovery of epithelial inclusions in uterine myomata, was one of the earliest indications of the

[1] *British Medical Journal*, 1901, vol. i., p. 814.
[2] Transactions of the Edinburgh Obstetrical Society, 1905, vol. xxx., p. 112.
[3] No. 4,627, Pathological Series.
[4] *Berlin. klin. Woch.*, 1882, vol. xix., p. 170.
[5] *American Journal of Obstetrics*, etc., October, 1899, p. 519.

correctness of this interpretation. The presence of these foreign elements was first demonstrated by Babès,[1] and Diesterweg,[2] in 1882; and their observations have since been confirmed and amplified by Shöttlander, Hauser, Ricker, Orloff, Recklinghausen, Meyer, Hirst, and others. They present either as solid cellular aggregations of various shapes and sizes, or as tubules, cysts, or structures not unlike utricular glands; in any case, the peripheral cells are of more or less columnar or cubical shape, and they may be ciliated. Many observers (Meyer, Tourneux, Ricker, Fischel, Coblenz etc.) have found similar epithelial inclusions—from which they believe certain cysts arise—in the otherwise normal uterine musculature.

By Babès and Recklinghausen these structures are believed to be Wolffian relics, while other pathologists insist on their Müllerian origin. But all such bodies are not necessarily either Wolffian or Müllerian *residua*,[3] for they may be included sequestra from the uterine mucosa itself. Indeed, Ribbert has found—deep in the uterine wall—not only sequestrated utricular glands, but even isolated fragments of the entire mucosa. In this connexion it is worth noting that, according to R. Meyer,[4] glandular structures are found in the mucosa, even as early as the seventh month of fœtal life, and they often penetrated deeply and were even aberrant; but this pre-natal origin for the uterine mucosal glands is, of course, contrary to the usually received opinion, according to which these structures are entirely of post-natal origin. In the face of Meyer's results, however, this opinion can no longer be maintained.

Heterotopic epithelial elements, are not present in all myomata, and the exact proportion of cases in which they occur has yet to be determined; the careful researches of Orloff, who examined serial sections of fifty-five specimens of small myomata, revealed only four instances of epithelial inclusions.

The researches of Coblenz, Meyer, Recklinghausen and others, have shown that the track of the utero-vaginal canal is strewn with epithelial débris, chiefly of Wolffian origin; hence, it is not surprising, in the process of building up the musculature, and in the coming together of the various ducts from the fusion of which the uterus and vagina result, that these aberrant epithelial elements are sometimes included in myomatous sequestrations; and no doubt the migrations and changed relations of the parts incidental to ontogeny, as well as the correlations between the musculature and its numerous bloodvessels, which are so extraordinarily interwoven, are also favouring factors. Such is the manner in which I believe the germs of myomata originate.

Some of those who have specially studied the subject, believe that germs of this kind also arise, by a similar process, during post-natal life; but, if this really be so, it has yet to be proved. So far as I can judge, the general drift of the ensemble of the evidence now available, is decidedly

[1] *Allgem. Wien. med. Zeitung*, 1882, Nos. 36 and 48.
[2] *Zeits. f. Geb. u. Gyn.*, 1883, vol. ix., p. 191.
[3] Evelt (*Münch. med. Woch.*, August 18, 1903) having reported an instance of melanotic malignant tumour, as primarily arising from a corpus myoma, this raises the question of ectodermal inclusions in such tumours; and, on the hypothesis of ectodermal "rests," other instances of primary uterine melanoma may thus be accounted for.
[4] "Ueber epitheliale Gebilde im Myometrium des fœtalen und kindlichen Uterus" etc. Berlin, 1902.

against this hypothesis : the germs of myomata always appear to be of pre-natal origin.

In this connexion it is well to remember, that myomata are not confined to the uterus and its vicinity, although they are of much more frequent occurrence here than elsewhere. Like their uterine congeners, the extra-uterine myomata are often multiple ; and they not infrequently contain epithelial—and more rarely other—inclusions.

If the foregoing views as to the origin of myomata be correct, it follows that extrinsic factors, such as local irritation and chronic inflammation—whether due to traumata, microbes, or other external irritants—play but a secondary part in their causation.

In concluding this subject, I have only to remark that malignant disease sometimes—but rarely—originates from myomatous tumours ; but of this more anon.

**Lipoma.**—Although fatty tissue is not normally present in the uterus, yet, as I have before mentioned, it is sometimes found included in myomata (T. Smith, Jacobson, Brünings, Seydel) ; moreover, instances of fatty tumours in the uterus have been reported (Knox, Stroinski, Busch, Orth, A. G. Ellis, Merkel [two cases], and Seeger). The only rational explanation of these heterotopic formations is sequestration, with displacement of fatty tissue matrix during the pre-natal period. Fatty tumours have also been found in the vicinity of the uterus—*e.g.*, in the broad ligaments (Treves, Prenice, Terrilon), round ligaments (Witte), recto-vaginal septum (S. Wells, Pelletan), tube (Parona), recto-uterine cul-de-sac (Laffore) etc. ; where they are just as heterotopic as in the uterus itself.

**Osteoma and Chondroma.**—The circumstances under which cartilaginous and osseous structures are met with in the uterus, are similar to those which condition the occurrence of fatty tissue in this organ, where such structures are always heterotopic. In the cervix of an otherwise normal fœtal uterus, R. Meyer [1] found a bony nodule, closely associated with a vestige of the Wolffian duct, through the medium of which it had evidently been introduced *ab extra* (Fig. 7). In this connexion, it is of interest to note that bone- and cartilage-containing tumours arise more frequently from this part of the uterus than elsewhere. This is specially obvious with regard to the peculiar forms of "mixed" sarcomata, to which this part is prone, whose structure comprises such various heterotopic structures, as cartilage, bone, striped muscle, fat, mucous tissue, epithelial elements etc., of which so many instances have been reported ; and I think there can be no doubt, that the germs of these tumours are aberrant elements sequestrated from the matrix of adjacent tissues during early pre-natal life. I have cited many examples of this kind, in my books on Uterine and on Vaginal Tumours. Gebhard has met with a malignant epithelial growth of this vicinity, whose stroma was studded with bits of hyaline cartilage. If malignant tumours of this locality were carefully examined, in serial sections, *ad hoc*, it would probably be found that aberrant elements of this kind are not particularly rare.

[1] "Knochenherd in der Cervix eines foetalen Uterus," *Arch. f. path. Anat.*, 1902, Bd. clxvii., S. 81.

Even as long ago as 1849, Lebert had—in two specimens—demonstrated the presence of true bone in uterine myomata; and, at about the same period, J. H. Bennet found cartilage; similar finds have since been made by Henle, Bidder, Freund, Ascher, Feuchtwanger, Johnston, and others; so that the occurrence of this kind of heterotopia is established beyond cavil. The only possible scientific explanation of such conditions, is the inclusion of osteo- and chondro-blasts in the nascent myomata, by sequestration from adjacent parts during early fœtal life.

In like manner, the remarkable proneness of uterine myomata to fibrification and calcification, probably depends upon the inclusion of

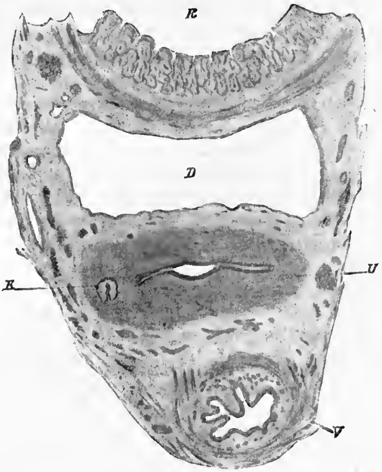


Fig. 7.—A Nodule of Bone in the Cervix of an otherwise Normal Fœtal Uterus (R. Meyer).

Transverse Section of the Pelvic Organs under a low magnifying power.

R, Rectum; D, Douglas's pouch; U, uterus; K, nodule of bone in the vicinity of the obliterated Wolffian duct; V, bladder.

heterotopic fibrinogenous and sclerogenous elements *ab extra;* for such proclivities are foreign to the normal uterine musculature.

The occurrence of osseous and chondromatous tumours in the uterus —of which instances have been reported by Miller, Seydel etc.—can only be interpreted on similar lines. In Miller's case, an osseous tumour occupied the site of the corpus of a malformed uterus, the patient being a girl, sixteen years old, in whom the vagina was absent.

Here it should be noted, that osseous and cartilaginous structures are also sometimes met with in sarcomatous tumours of the uterus, other than those peculiar forms above referred to, of which instances are given in my book on "Uterine Tumours."

Bone and cartilage-containing tumours have also been met with in the vicinity of the uterus, *e.g.*, in the ovary (Baet, Barnes, Donati, etc.), in the broad ligament (Kaul-chondrifying sarcoma), and in the recto-uterine cul-de-sac (Hugenberger).

**Cysts.**—Very interesting in this connexion is the little-studied subject of cyst-genesis in the uterus ; for, nearly all formations of this kind undoubtedly arise, as the outcome of pre-natal developmental irregularity.

The discovery of aberrant epithelial inclusions of various kinds in the uterine wall and its vicinity, to which I have previously referred, enables us to understand the sources whence many uterine cysts arise. These heterotopic elements have been described by various authors as of Wolffian, Müllerian and mucosal origin ; and probably all these sources are represented in the germs of uterine cysts. As many recent researches have shown, the track of the uro-genital *anlage* is strewn with débris of this kind.

The commonest uterine cysts undoubtedly are the small multiple ones of the cervix and its vicinity, which only occasionally increase to such a size as to merit the name of disease. The histological structure of these cysts, as well as the peculiar nature of their fluid contents, enable us to recognize their identity with the glands of the cervix, of which they are obviously sequestrations. The well-known *ovula Nabothii* are the prototypes of these cysts, which R. Meyer has discriminated in the pre-natal period.

In the antero-lateral part of the cervix and the adjacent parts of the uterus, cysts are occasionally found—lined by a single layer of cubical epithelium quite different from that of the glands of the cervix—which, it appears certain, are derived from the cystic distension of unobliterated portions of the Wolffian duct (Gartner's), such as Meyer, Nagel, Tourneux, Rieder, and others, have discovered in this vicinity. In pre-natal life, Meyer found that these vestigial remains were more extensive, and of more frequent occurrence, than after birth. Cysts of this kind—some of them congenital—have been studied by Burckhardt, Senn, Klein, Rieder and many others.

We are indebted to the admirable researches of Coblenz,[1] the significance of which are even now not fully appreciated, for recognition of the fact that papilliferous cysts may develop anywhere along the course of the Wolffian (Gartner's) ducts ; and he has also shown that the germs whence these cysts arise are Wolffian residua—derivatives of the paroöphoron, or, as is rarer, of the epoöphoron. The work of Recklinghausen, Meyer, Pick, Landau and others, confirms and extends Coblenz' results.

Residua of this kind have been detected in the otherwise normal uterine musculature by Coblenz, Ricker, Rieder, Meyer, and others ; and, in the adjacent structures—*e.g.*, broad ligament, round ligament, pelvic connective tissue, tube, ovary etc.

As examples of cystic tumours arising in the uterine walls from these Wolffian residua, reference may be made to Czerwenka's case of " cyst-adenoma papillare proliferans " ; to Gusserow's case of " cystic adenoma " ; to Ahlfeld's case of " kystoma multiloculare " of the cervix and portio

[1] *Arch. f. path. Anat.*, 1881, Bd. lxxxiv., S. 26.

etc., as well as to older cases of like nature reported by Cruveilhier, Lebert and Rokitansky. Meyer has met with a large congenital tumour of this type, in an eight-month fœtus, which had evolved in close proximity to Gartner's duct.

A congenital polycystic condition of the corpus uteri, with cystic adeno-myoma of the cervix, has been described by Woskresensky; and Mears[1] has reported a remarkable case in which congenital polycystic changes affected the uterus, ovaries, and kidneys simultaneously, as if owing to some developmental irregularity affecting the evolution of the whole Wolffian body.

Similar cystic papilliferous tumours have been met with in the vagina, in the para-uterine and para-vaginal connective tissue, in the broad ligaments, round ligaments etc.

Here also mention may be made of the fact, that in nearly all of the above-mentioned localities myomatous tumours, comprising well-marked Wolffian residua—the so-called "mesonephric myomata"—have lately been discriminated.

Since these papilliferous and other cystic tumours are identical in structure with the ordinary forms of ovarian cystoma, the important inference may be drawn, that these ovarian cysts also arise from included Wolffian residua; as to which it seems to me the cumulative evidence from various sources is so strong, as to be practically conclusive. And in the same category, I doubt not, congenital polycystic disease of the kidneys should be included. It would require more space than is here available to fully prove this thesis; but I have at hand all the evidence for doing so. As an indication of the correctness of this interpretation, reference may here be made to the obvious correspondence between the different forms of ovarian and broad-ligament cysts, which holds good even for dermoids.

**Dermoids.**—The researches of Sänger have made it perfectly clear, that dermoids do originate in the pelvic connective tissue and adjacent structures, quite independently of the ovaries. Thus, formations of this kind have been found in the pelvic connective tissue (Höfer, Germain, Sänger); between the vagina and rectum (Mahomed, Mannel, Merriman); between the cervix uteri and rectum (Emmet, Cartez, Barette, Beyea); between the bladder and uterus (Küster, Sänger, Charcot); in the urethro-vaginal septum (Englisch, Wiggin); in the tube (Pozzi, Treub, Ritchie, Orthmann); in the broad ligaments (Abel, Marshall, Lunn, Gottschalk, Rendu, Höfer etc.); in the round ligament (Rendu); in the vagina (Watts, Veit); while in the bladder and rectum many such cases have been reported.

In several of the sites of these pelvic dermoids, ectodermal "rests" have been detected in fœtal or early post-natal life; *e.g.*, in the broad ligaments by Meyer, Switalski, Ribbert (Fig. 8, next page), and Marchand; in the pelvic connective tissue (especially in and in the vicinity of the lymph-glands) by Wakefield; in the musculature at the neck of the bladder by Meyer etc.

I am not aware that extrinsic ectodermal elements of this kind, have

[1] *Philadelphia Medical Times*, U.S., 1872, p. 314.

hitherto ever been detected in the otherwise normal uterine parenchyma; but it is, nevertheless, tolerably certain, if the cervix were systematically examined *ad hoc*, that such would be found. The presence of epidermoidal elements in certain sarcomata of the lower part of the uterus, as in cases described by Hauser, Rosenstein etc., points to this conclusion; and of like significance is the occurrence of melanotic elements in sarcomata of this part, as described by Whitridge Williams, Johnston etc., and in a uterine myoma by Evelt.

Very little is to be found in pathological publications, as to uterine dermoids; indeed, until Sänger (1890) had made it perfectly clear that these formations do originate in the pelvic connective tissue, quite inde-

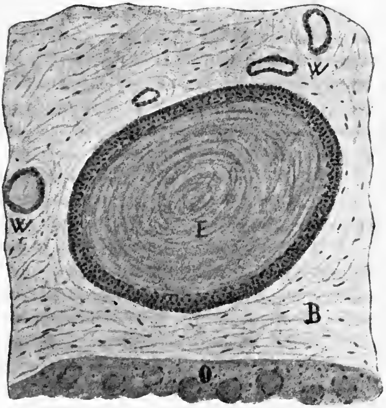


Fig. 8.—A Heterotopic, Hornifying, Epidermoidal "Rest" in the Broad Ligament (Ribbert).

E, The aberrant epidermoidal nodule; B, Connective tissue of the broad ligament; O, ovary; W, W, Wolffian tubules.

pendently of the ovaries, the possibility of such occurrences was generally disbelieved. With such facts as those above cited before us, it would, however, now be unreasonable to maintain such a sceptical attitude. In comparatively recent times, examples of the simplest form of uterine dermoid cyst, with sebaceous or cholesteatomatous contents, have been studied by Ahlfeld, Cornil, Allen, French, Recklinghausen, and Shoemaker; in the older publications, examples of somewhat more complicated forms (piliferous) are recorded by Vicq d'Azyr and Fabricius Hildanus; and, in recent times, teeth and hairs, as in Stewart's case; while, a few years ago, a still more complicated tumour of this kind was described by Geyl:[1] this formation was connected with the posterior part of the vaginal fornix, and besides skin, it comprised such diverse structures as bone, striped muscle, fat, nerve etc.

At an early stage of pre-natal development, the Wolffian duct is in

[1] *Samml. klin. Vorträge*, N.F., No. 190, 1897.

such close proximity to the ectoderm, that many embryologists now maintain its ectodermal origin. However this may be, it is certain that in its subsequent migration, this duct may carry away with it ectodermal elements, which may thus be lodged in the uterus, pelvic connective tissue, ovary or other pelvic organs, where dermoid cysts have been found. It is to foreign elements thus imported during early pre-natal life, that we must ascribe the germs of these various dermoid tumours.

Ovarian and other dermoids are known to have marked proclivity to originate malignant disease, but hitherto no instance of this kind has been reported in connexion with these pelvic dermoids, unless an old case by J. S. Bedford : " Sarcomatous Tumour of the Uterus containing Hairs and Stearine," is of this nature ; but several examples of primary malignant epithelial and connective-tissue tumours of the pelvic areolar tissue, obviously of heterotopic origin, have been met with (Heinsius, Herff, W. M. Smith and Kaul—chondro-sarcoma).

The probable origin of certain uterine and vaginal tumours from " rests " of the Müllerian ducts, that have failed to fuse and blend in the formation of the utero-vaginal canal, was first suggested by Freund. He described myomatous cystic tumours of this kind, as occurring in the lower part of the uterus and the upper part of the vagina, especially posteriorly.

Similar formations have been met with in the para-uterine connective tissue (Verneuil, Haussmann). A single layer of columnar epithelium, which is often ciliated and may present involutions and cysts, lines the interior of these tumours. There are generally traces of concomitant uterine duplicity, *e.g.*, uterus bicornis septus etc. Instances of congenital tumours of this kind have been reported by Briesky, and others.

Myomatous uterine tumours, having in their interior diverticula communicating with the uterine cavity, as in cases of uterus accessorius—bifid, trifid uterus etc.—have also been reported (Brens, Neugebauer, Ricker, Recklinghausen, Meyer, Höllander, Skene, Delpage and others). Such conditions appear to be due to abnormal myomatous growth, around persistent diverticula from the Müllerian ducts of pre-natal origin. Tumours of this kind are, however, far from common ; and it seems to me improbable from consideration of the ensemble of the subject, that the ordinary myomata arise from Müllerian " rests." In this connexion it should be borne in mind, that the Müllerian ducts have no proper musculature of their own, the elements whence this is derived being superimposed *ab extra*.

Another form of uterine cyst, of which many examples have been recorded (Leopold, Fehling etc.), is the endothelial-lined formation, which is generally believed to be of lymph-angiectasic or telangiectasic origin. It is well, however, to recollect that Meyer specially noted the frequent invagination and inclusion of small peritoneal pouches, into the nascent uterine wall during pre-natal life ; and it is probable that these inclusions are the germs whence most cysts of this kind originate. It accords with this mode of origin, that Hahnsseau has lately reported instances of this variety of cyst, caused by the traumatic inclusion of peritoneum in wounds made during operations on the uterus and its adnexa.

**Sarcoma.**—In the foregoing dissertation, I have proved that the germs of all non-malignant uterine tumours are the outcome of developmental irregularity, during pre-natal life. Did time and space permit, I could adduce equally conclusive proof, that the *anlagen* of all non-malignant tumours—wherever arising—are similarly conditioned.

This being so, an *a priori* assumption is inevitably raised, that the germs of malignant tumours may also be similarly conditioned. Hence we now have to focus our attention on this aspect of the subject, so far at least as malignant tumours of the uterus are concerned.

I have already had occasion to indicate several instances in which the heterotopic findings, revealed by histological analysis of tumours of this kind—together with other facts of like import—pointed clearly to pre-natal origin; and most of these tumours were sarcomatous.

Taken as a whole, a surprisingly large proportion of uterine sarcomata are found, on careful examination, to bear the impress of the pre-natal stamp.

Practically all of the important group of "infantile" sarcomata [1]—whether of the lower part of the uterus or of the vagina—must be included in this category. These tumours are often congenital, or they occur very early in life; they are frequently multiple *ab initio*, and accompanied by multiple polypi; while other adjacent organs, besides the one primarily involved, may be concurrently affected. Their structure commonly comprises various heterotopic elements, such as striped muscle cells, epithelial islets, leiomyomatous cells and myomatous tissue. These various indications point conclusively to their origin from pre-natal developmental irregularities; and it should be noted that of the parts apt to be involved, all are more or less concerned in the formation of the cloaca; indeed, it is with the formation of this structure—even more than with that of the uterus—that the germs of this curious disease originate by sequestration and inclusion, during the various processes of approximation and fusion of the constituent parts involved therein.

Another considerable group of uterine sarcomata, which recent research has shown to be much less rare than was formerly believed, is the grape-like or botryoidal variety of adults; which is—with few exceptions—a malady of the lower part of the uterus. In this, as in some other respects, the malady resembles the infantile variety; but, unlike the latter, initial multiplicity—especially in adjacent organs such as the vagina, bladder and rectum—is hardly ever seen. Hence it may be inferred that the developmental irregularity concerned in its genesis, appertains to the cervix proper rather than to the cloaca. With this reservation, the difference in age incidence, and also the different nature of the concomitant heterotopic inclusions, *e.g.*, cartilage and bone, these two forms of disease have much in common.

The structure of this peculiar type of sarcoma commonly comprises

[1] For details of illustrative cases the reader is referred to my publications on "Uterine Tumours," p. 322, and on "Vaginal Tumours," p. 25.

such various heterotopic constituents as striped muscle, cartilage, bone, various types of epithelial elements, mucous tissue etc.; which, it may be inferred, from what I have previously mentioned as to the developmental anomalies of this part, arise from aberrant elements sequestrated from the matrix of adjacent tissues during pre-natal life, and included in the nascent organ, probably through the agency of the Wolffian duct in most cases.

Judged by the results of their histological analysis and general morphology, the remaining uterine sarcomata may be regarded as derivatives of the mucosa, or of the parenchyma of the uterine wall. As to the pre-natal origin of the germs of these mucosal tumours, we have only a few —but significant—indications; *e.g.*, Wagner, Geissler and Reid have found chondromatous structures in them; Whitridge Williams, Johnston, Taylor, Rokitansky and others, melanotic elements, which can only be accounted for as ectodermal inclusions. As to the occasional association of tumours of this kind with various gross uterine malformations, I shall have to refer to it in the sequel. With regard to the sarcomata of parenchymatous origin, some of these undoubtedly arise from myomata —which, as we have seen, are of pre-natal origin; and, in this connexion, we must not forget Evelt's case of malignant melanoma primarily arising in a myoma, to which reference has previously been made. Moreover, in these tumours cartilaginous and epithelial "rests" are occasionally found, which could only have originated during pre-natal life. It is to this latter source, that we must refer the germs of the various remarkable cystic sarcomata of parenchymatous origin; thus, in a case by Aslanian, a large multilocular, telangiectasic cysto-sarcoma of this kind, was concomitant with abnormal persistence of the Wolffian body; while Coblenz has seen sarcoma of the uterine parenchyma concomitant with a unilocular papillary cyst of the right ovary, and multilocular cystic disease of the left ovary.

Of like import are the cases of mixed malignant tumours—forms in which epitheliomatous and sarcomatous processes go on simultaneously— of which instances have been reported in the uterus by H. R. Spencer, Maier, Kuhnart etc.

Taking all these various indications into consideration, it seems to me impossible to avoid the conclusion, that the germs of all uterine sarcomata are probably the outcome of developmental irregularity of pre-natal origin.

**Malignant Epithelial Tumours.**—From what has been previously stated, it will be gathered that histioid tumours are never of such a monstrous nature, as not to present some analogy to the pre-existing structure of the parts whence they originate, either in their pre- or post-natal states; and this holds also for malignant epithelial tumours, as I shall now proceed to show. Moreover, it is not only the constituent cells of these tumours, wherein the essence of the disease resides, that manifest this similitude; but also the connective-tissue stroma or framework, wherein they are set. Thus may be explained the great structural diversities, that obtain between the malignant epithelial tumours of different parts, and of different tissues, according to the sites whence they originate, which is such a marked feature of all tumours of this kind. What, for instance, can be more divergent in this respect, than the appearances presented on microscopical examination by sections of cancers from such different parts as the breast, the rectum and the skin? We learn from such studies, that malignant epithelial new formations always present unmistakable histological resemblance to the structures whence they originate. And this resemblance can also be traced in the physiological properties of their constituent cells; for, as Waring[1] has demonstrated, the cells of cancer of the stomach and pancreas produce the same ferments—pepsin, trypsin, etc.—as the normal secretory cells of these organs.[2] In like manner, Johannes Müller, more than half a century ago, proved the presence of casein in cancers of the female breast; and the abundance of fatty matters contained in the cells of these neoplasms is well known. We are thus reminded of the similar metamorphoses that the cells of the normal gland undergo during lactation; but, the nearest approach to normal secretion, that the tumour structure ever produces is a scanty mucoid fluid, presenting some resemblance to a poor kind of colostrum. Such a result is quite in accordance with the experiments of Martinotti, which show that the cells of secretory glands when in a state of active growth and proliferation, tend to lose their normal secretory aptitudes—there being a certain antagonism between proliferative and secretory changes.

Similarly, cancers of the cervix uteri may be expected to yield indications of the presence of substances identical with the cervical mucus; and, in this respect, they will probably be found to differ from cancers of the corpus. As tending to confirm this expectation, it may be mentioned that Cornil and others have observed, in the constituent cells of cervical cancers, indications of mucoid or calyciform changes, similar to those that are so characteristic of the epithelium of the cervical glands during the elaboration of their peculiar secretion.

The cornifying properties of epidermoidal cancers of the skin, likewise exemplify the same peculiarity.

The characteristics of the stroma of cancerous tumours, are chiefly determined by the pre-existing structure of the affected part. Its alveolar disposition, which was formerly regarded as the histological criterion of cancer, is now known to be merely a local peculiarity.

In its minute structure and general characters, the stroma of mammary cancer closely resembles the stroma of the normal gland, of which it is evidently a derivative. It consists of thick bands of dense white fibrous tissue, containing elastic fibres and anastomosing connective-tissue cells, which are specially numerous at the meeting-points of the diverging bands. The characteristic hardness of mammary cancer is mainly due to its abundance and density; in fact, hard cancers are the dominant forms that arise from regions rich in fibrous tissue. Moreover, it is noticeable that elastic fibres are met with in great abundance in cancers that arise from structures normally rich in them, such

[1] *Journal of Anatomy*, October, 1893, p. 142.

[2] In pancreatic cancers, besides trypsin, Waring found amylopsin, steapsin, and a milk-curdling ferment.

as the breast and skin. Müller attributes the large amount of gelatin found on analysis in mammary cancers, to the abundance of its fibrous stroma.

On the other hand, the stroma of uterine cancers consists of scanty fibrillar tissue, like that met with in the normal uterine mucosa, which it further resembles in that it usually contains unstriped muscle cells. Hence little or no gelatin is found in uterine cancers.

Another marked characteristic of cancerous tumours that must be mentioned here, is the great resemblance always noticeable between the primary and secondary growths, the significance of which it is impossible to ignore. As Moxon has sagely remarked: "The first cancer which appears has a likeness to the part in which it appears, and the secondary cancers arising from it have the likeness of that first cancer; and those who doubt that they come from that first cancer must show us why they have that likeness." In this connexion Waring's observations are of great interest, for they show that the same physiological properties are manifested by the cells of the secondary, as by those of the primary growths. In short, the secondary growths repeat the distinctive characters of the primary growth with such fidelity, that the seat of the latter may often be correctly surmised by careful examination of the former.

Bearing in mind these considerations and what they imply, we are now in a position to come to closer quarters with the question of the genesis of uterine cancer.

Insuperable difficulties surround the investigation of the very earliest stages of primary cancer formation; but, in the formation of secondary cancers, nature is constantly performing the miracle of cancer genesis under our very eyes, and in a manner that admits of scientific investigation. There are good reasons for believing that primary cancers arise, exactly as do these secondary formations; so that, by investigating the latter, we may be able to elucidate the former.

Now, the most important fact revealed by the study of the origin of secondary cancer is, that the germ whence it arises—which must be very small—is not a normal constituent of the affected part, but an intruder *ab extra*. Can the like be said of the germ of primary cancer? The histological analysis of primary cancers of the uterus shows that the majority of these tumours consist of structures, which have remarkable similitude to those normally comprised in the mucosa of the part; and from this it follows, that the germs of these tumours must be derivatives of this structure—whether of pre- or post-natal origin.

Thus, the only kind of heterotopia that can be admitted for the germs of these uterine cancers, is a local heterotopia, referable to developmental irregularity of the mucosa itself. In this restricted sense, as I shall proceed to show, the germs of most uterine cancers are decidedly heterotopic, that is to say, they are not direct derivatives of the normally integrated, pre-existing cells of the part.

The great majority of uterine cancers arise in the cervix; and, among these tumours, it is not uncommon to meet with forms, which, on histological examination, present no recognizable similitude either to the glandular or to the epidermoidal structures of the cervical mucosa. The germs of some of these tumours may be as truly heterotopic, as those of the secondary cancers; that is to say, they may be derived from ectodermal elements sequestrated during early pre-natal life, and included in the nascent uterus with the Wolffian duct; or, it is even conceivable, that they may be "rests" of this latter structure. We know that tumours of this kind and thus derived, do form in parts adjacent to the uterus, such as the pelvic connective tissue etc.; and, therefore, it seems not unreasonable to infer that they may also originate thus in the uterus itself. It may even be surmised, that the undue proclivity of this part of the uterus to malignant epithelial tumours, is explicable in this way.

However this may be, the fact remains that the histological elements of most uterine cancers so closely resemble those normally met with in the uterine mucosa, that we may classify them as being either of the cylinder-celled or epidermoidal type.

The mucosa of the uterine cavity is lined throughout by a single layer of cylinder-shaped epithelial cells; and the innumerable glands which open on its surface, are the result of follicular depressions of this epithelial lining into the sub-mucosa. In the midst of this cylinder-celled epithelial lining of the corpus uteri, small islets of aberrant epidermoidal cells, have often been detected (Ries, Zeller, Schuchardt, Fritsch, Friedländer etc.); and probably this condition is fairly common. Once this fact has been grasped, there can be no difficulty in recognizing these heterotopic elements, as the germs of those hornifying epidermoidal cancers of this part, of which examples have been reported by Gellhorn, Ries, Piering, Gebhard, Keith, Flaischlen, Lohlein, Emanuel, Kaufmann and others. In several instances of initial multiplicity, epidermoidal cancer has been found coexistent with cylinder-celled cancer of the same uterus (Hofmeier, Winter, Schauta etc.); and some cases have been reported, in which the two kinds of epithelium were associated in the same tumour (Hirschmann).

The mucosa of the cervix, as to its upper two-thirds, is lined by a single layer of cylindrical epithelial cells; whereas, a laminated, flattened, epidermoidal type of epithelium—which is an upward extension of that covering the portio—lines more or less of its lower part; at least, this is the usual condition in multiparæ, in whom the flattened cells of the portio are prolonged for a variable—often considerable—distance, within the *canalis cervicalis.* It is probable that the heterotopic epidermoidal cells found in the mucosa of the corpus, are detached aberrant offsets from these upward extensions of the portio cells, sequestrated during pre-natal life. It accords with this, that Villiers and Thérèse have demonstrated, in the midst of the cylinder-celled lining of the cervical mucosa, detached islets of epidermoidal cells, with Malpighian stratum etc., where they presented as whitish plaques. Such no doubt are the germs, whence the considerable number of epidermoidal-celled cancers of this part of the cervix arise.

In its structure, the lining membrane of the portio differs from that of the rest of the uterus, resembling rather that of the vagina. Similarly in its proclivity to neoplasms, it likewise takes after the vagina. As the portio projects into the vagina, it is, in fact, capped by an upward extension of the epidermoidal-celled, dermo-papillary, vaginal lining membrane. In the development of papillated structures like the portio, the epidermis plays an important part. It causes these structures to arise by processes of its proliferous cells, growing into the subjacent mesoblastic corium. In this process, "rests" of these ingrowing epidermoidal processes are commonly sequestrated, and included in the nascent corium; where, in post-natal life, they may subsequently be recognized by histologists as "pearls," or other non-integrated epidermoidal structures. Pre-natal "rests" of this kind, are of common occurrence in and beneath the corium of the portio and adjacent structures. As we have seen, epidermoidal elements of this kind are the germs whence many cervical and some corpus cancers arise; hence, it may be inferred that it is to this source, rather than to the normally integrated elements of the mucosa of the portio, that we must look for the germs of most epidermoidal cancers of this part.

In addition to this variety of epithelioma, other forms also originate from this part of the uterus. Under certain pseudo-pathological conditions, which I will now proceed to describe, the cylindrical epithelium of the cervix encroaches upon the epidermis-covered territory of the portio; and, from this foreign element, cylinder-celled cancers arise, analogous to those that spring from the cervix. So common is this invasion of the portio, that the majority of its cancers originate from this source.

It seems probable that most of these aberrant elements, are the outcome of pre-natal developmental irregularities. At an early stage of embryonic life, the upper part of the vagina, as well as the cervix, is lined by cylindrical epithelium. In the subsequent transformation to the flattened variety, minute islets of the original cylindrical cells may still persist unchanged. Klotz and others have demonstrated conditions of this kind in adults; while Fischel has shown that in young infants, cylindrical epithelium is usually found occupying the portio, for a considerable distance beyond the os externum.

An analogous condition results from the invasion of the portio by offsets of the cervical glands (the so-called "erosions"), which so frequently appear during post-embryonic life in consequence of hyperplastic changes; as well as from the somewhat similar state that ensues from partial prolapse ("ectropion") of the cervical mucosa—whether merely the result of tears etc., during parturition, of cystic disease, or of other pathological states. Moreover, the minute cysts ("ovula Nabothii") so frequently met with in the lower part of the uterus, which are obviously sequestrations from the glands of the cervix, must also be borne in mind, for cancers have been shown to originate from them.

Here it may be mentioned that Nichols[1] has produced cysts of this kind experimentally, by transplanting grafts of the uterine mucosa into various situations.

Recent researches indicate that these acquired forms of heterotopia, like those previously mentioned, are also really of pre-natal origin, the

[1] Third Report of the Croft Cancer Committee, Boston, U.S., 1905, p. 117.

inherent flaw simply being made manifest by the supervention of other pathological changes. Even " lacerations " may often be of embryonic origin, for Fischel has demonstrated the occurrence of congenital fissures, in exactly the situations usually occupied by these so-called lacerations.

From the foregoing it will be gathered, that in all cases in which we have been able clearly to trace the genesis of cancer in the different parts of the uterus—corpus, cervix and portio—the germs of such tumours have proved to be, not the normally integrated, pre-existing, epithelial cells of the part; but rather non-integrated " rests," detached from their normal connexions during pre-natal life. This being so, we are I believe fully justified in assuming, that the germs of all malignant epithelial uterine tumours are similarly conditioned; indeed, the more carefully we consider the significance of the ensemble of ascertained facts and indications as bearing on this subject, the more strongly is the truthfulness of this conception impressed upon us.

In short, I think there can be no doubt, that pre-natal developmental irregularity presides at the genesis of all uterine tumours.

### Uterine Tumours, and Gross Developmental Irregularity of the Uterus etc.

I now pass to the consideration of the connexion between uterine tumours, and certain gross developmental irregularities of the uterus and other parts, with which these tumours are fairly often concomitant. In the absence of the requisite data, it is for the present impossible to ascertain the exact proportion of cases in which this concomitancy occurs. It would, however, be a mistake to suppose, on account of the comparatively few instances of this kind noted by the older gynæcologists, who made special studies of uterine malformations (Kussmaul, Fürst etc.), that this concomitancy is rare; for, in those days, when the teratological aspect of the subject was the only one in the specialist's mind, it is hardly likely that the presence or absence of tumours would have attracted much attention. It accords with this, that of six specimens illustrative of uterine malformations, in the broad-minded Cruveilhier's great work,[1] two were complicated by myomata and one with double ovarian cystoma. But the best proof of all is, that within the last few years over a hundred instances of this concomitancy have been recorded. Hence, it seems to me as clear as it possibly can be, short of actual demonstration, that these developmental irregularities predispose to tumour formation.

**Myoma.**—Uterine duplicity is the commonest type of malformation concomitant with myomata; and some idea of its frequency may be gathered from the fact, that without any attempt at an exhaustive search, I have gathered notes of over fifty cases. In this list all the different grades of duplicity are represented, from the most complete type as represented by *uterus didelphys* (cases by Clay, Galabin, G. B.

[1] *Anat. Path. du corps humain,* 1829-1833, t. i., liv. iv., pl. v.

Johnston, Lewers, Graverry, Mundé, Lyle, Pick etc.), to the least as represented by uterus introrsum arcuatus (Flatau). But most cases are met with in *uterus bicornis*, which is the commonest variety of this type of malformation (Foisy, Falk, Eberlin, Doran, Lockyer, Gow, Boni,

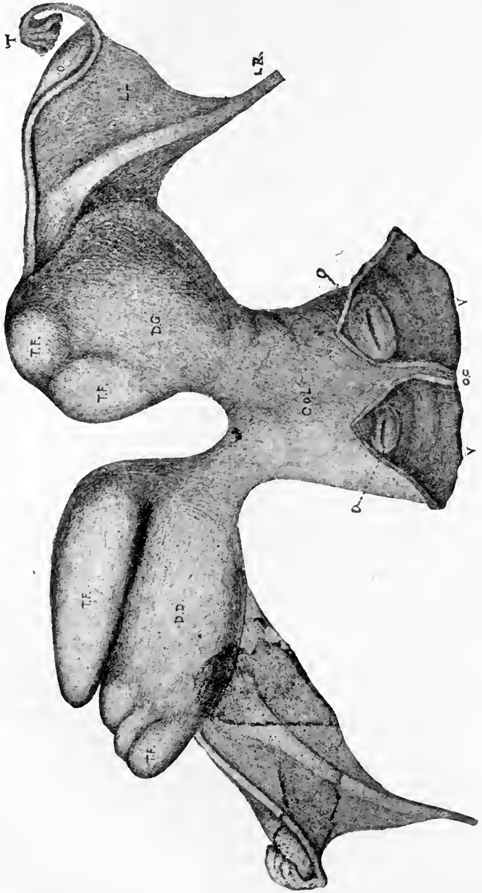


FIG. 9.—UTERUS DUPLEX, WITH MULTIPLE MYOMATA (CRUVEILHIER).
DD, DG, Corpus uteri divided into two horns; LL, broad ligament; LR, round ligament; T, tube; O, ovary; TF, TF, several myomata in each uterine horn; COL, the septate cervix; CC, the septa; O, O, the two os uteri; V, V, the double vagina.

Martin, Meurer, Gunsett, Wagner, Heinricius, Cruveilhier, Snegurieff, Gibson, Clark, Pauchet etc.).

In an interesting case by Clay,[1] double uterus and vagina was associated with uterine myomata, and absence of one kidney. In a

[1] *Lancet*, 1877, vol. ii., p. 87.

uterus didelphys, Czerwenka[1] found two myomata of the left corpus, concomitant with cancer of the left cervix.

In G. B. Johnston's case,[2] one compartment of the double uterus contained a full-term fœtus, which was delivered by Cæsarean section, while the other compartment was merged in a large myoma, which was removed, with the malformed organ, by hysterectomy. In *uterus bifidus*, Pauchet found right-sided myoma, with left-sided pregnancy.

Pick[3] has reported cases in which the myomatous tumour lay in the septum, between the bodies of the two uteri ; and other cases of this kind have been met with by Lockyer,[4] Clark, J. Schmidt (adeno-myoma), Gunsett etc. In these cases, the germ of the tumours must have been in position, as early as the second month of pre-natal life, when the coalescence of the Müllerian ducts begins.

Several instances of the development of myomata in the unicorn uterus have also been reported of late : *e.g.*, in the rudimentary horn by Routh, Doran, Mackenzie, Romiti, Mangiagalli etc. ; in the developed horn by Bland-Sutton ; and in the cervix, which was replaced by a mesonephric adeno-myoma, by Josephson etc.

In some of the foregoing cases, the vagina also was absent or atresiac (Mangiagalli, Eberlin) ; while cases reported by Martin, Jenks and Guyot, were concomitant with vaginal absence, the uterus being normal.

Uterine myomata have also been found in association with congenital atresia of the uterus (Dreykorn), congenital ante-flexion (Thomas), in the " infantile " uterus (Keiffer) ; while Jackson has reported myomata of an atresiac " infantile " uterus, in which cancer was also present.

But the most remarkable instance of this type known to me, is the case reported by Lynds,[5] in a woman aged forty-five, with a large myoma of three years' duration, occupying the site of the absent uterus ; who had, nevertheless, lived for nineteen years in wedlock without being aware of any physical defect, although she had never menstruated and had never been pregnant. It was found, in the course of the operation, that the vagina also was absent, as well as all the uterine appendages ; and, of the ovaries, the only trace was a small rudiment of one.

I have previously referred to myomatous tumours connected with such malformations as uterus accessorius, bifid and trifid uterus etc.

In a pseudo-hermaphrodite, aged fifty, in whom the female type appeared to predominate, Grüner found myomata of the malformed uterus ; and, in another person, aged forty-nine, with a similar defect, Howitz met with a tumour the size of a cocoanut, due to myomatous disease of the unicorn uterus. In the latter case the left tube was absent, the ovaries were represented merely by small nodules, remains of Gartner's ducts were found in the vaginal walls, and there was hypospadias with hypertrophy of the clitoris. Neumann has described myomata of the uterus and tube, concurrent with Wolffian " rests " in both ovaries ; and Russell has reported the finding of Müllerian relics in

[1] *Monats. f. Geb. u. Gyn.*, Bd. xx., Heft 5.
[2] Trans. Southern Surg. and Gyn. Association, Richmond, Va., U.S., 1900.
[3] *Monats. f. Geb. u. Gyn.*, October, 1897 ; also *Arch. f. Gyn.*, 1896, Bd. lii., S. 389.
[4] *British Journal of Obstetrics*, etc., 1905, vol. vii., p. 172.
[5] *Journal of the Michigan State Medical Society*, U.S., March, 1905, p. 122.

the ovary, whence structures like utricular glands had evolved, resembling the epithelial inclusions found in some myomata. Wetherill, in removing a large myomatous uterine tumour, noticed supernumerary oviducts and hydatids.

This leads me to remark on the frequency with which uterine myomata are complicated with *ovarian cystomata* (often bilateral), dermoids, and cysts of the adnexa—broad ligaments, round ligaments, etc.

Of his operated uterine myomata, Péan found associated ovarian cystomata in 12·5 per cent.; and of Winckel's ovarian cystoma, 18 per cent. were concurrent with myoma uteri.

In a remarkable case reported by Buffett, the combined weight of the associated tumours amounted to no less than 216 pounds, the left ovarian cystoma weighing 180 pounds, and the uterine myoma 36 pounds.

In the case of a negress, with an enormous cystic myoma weighing 135 pounds, as described by Stockard, the uterus also contained several solid myomata ; and besides there was a small myoma of the left Fallopian tube, a cyst of the corresponding broad ligament, and cystic disease of the left ovary.

Leo has found myomata of the uterus coexisting with cystoma of the right ovary, and polycystic disease of the left kidney. I have previously had occasion to refer to Mear's case, in which the uterus, ovaries and kidneys were concurrently affected with congenital polycystic disease, as if from some developmental irregularity involving the whole Wolffian body. Flatau has found a similar type of cystic uterine disease concomitant with myoma of that organ ; while Doléris and Algret report the concurrence of uterine myomata, with congenital polycystic disease of both kidneys.

Thornton has seen multiple uterine myomata associated with a large multilocular cystoma of the right ovary, a cyst of the right broad ligament, and multiple cysts of the left ovary ; and, in Hodge's case, uterine myomata were associated with cystic disease of the ovary and broad ligament.

Dartigues and Claisse have reported an instance, in which a large uterine myoma coexisted with an enormous multilocular cyst of the left ovary, and a dermoid of the right.

Emmet has seen a large cystic myoma of the fundus, with several sold myomata adjacent to it, and a polypoid intra-uterine myoma, concomitant with multilocular cystoma and dermoid of the right ovary. In many cases, uterine myomata and ovarian or broad-ligament dermoids, have been found concomitant (Porter, Mauclaire, Hulke, Gottschalk etc.).

Amann mentions the association of adeno-myoma of the uterus with ovarian dermoid ; Cartez has found uterine myomatous disease, concomitant with a piliferous dermoid of the connective tissue, beneath the peritoneum of Douglas's pouch ; and Berger met with a para-uterine, piliferous pelvic dermoid, which comprised a piece of bone bearing two teeth, concomitant with myoma of the corpus uteri.

Fatty tumours of the para-uterine connective tissue, in association with myoma uteri, have been described by Roux and Ullman.

Myomatous tumours of the uterus, with bipartite bladder, have been reported by Knox; and by Garrigues, the same disease has been seen with the fœtal type of bladder. Thorne found uterine myomata coexistent with ossifying myoma of the bladder.

The frequency with which uterine myomata are multiple, might of itself lead us to suspect the association of developmental irregularity, with the origin of these tumours; and the occurrence of instances in which the whole musculature is converted into a dense mass of small tumours, to which I have previously called attention, points to the same conclusion.

Of like import is the finding of uterine myomata concomitant with similar tumours in the ovary, broad ligament, round ligament, tube, vagina, and in other situations adjacent to the uterus, of which many examples have been recorded.

Thus, Neill has met with a case in which myomata coexisted in the uterus, broad ligaments, and ovaries; while Virchow long ago reported an instance in which the uterus, ovary and vagina were concurrently affected.

**Epithelioma (vel Carcinoma).**—In like manner with the foregoing, I know of many instances in which primary malignant epithelial tumours of the uterus, have been found in association with gross local developmental irregularities.

Thus, examples of the concurrence of cancer of the cervix with the various forms of uterine duplicity, have been recorded by Czerwenka,[1] Rossa,[2] Pollosson,[3] Huber,[4] Biehl,[5] Zweifel,[6] Hasse,[7] Janvrin, Orthmann, Alexander, Wertheim, Penrose, Vineburg and others. In cases by Czerwenka and Jackson, both cancer and myomata were associated concurrently with uterine developmental defects.

Instances of cancer of the unicorn uterus have been reported by Heinricius and Josephson. In a patient who died of cancer of the colon, Mackenzie found a myomatous tumour of the one-horned uterus.

In a case of vaginal atresia, Sandheimer met with cancer of the corpus uteri; and Neugebauer has seen uterine cancer, in a pseudo-hermaphrodite with hypertrophy of the clitoris.

The concurrence of vaginal cancer and uterine myomata, has been noted by Warder. In a patient with cancer of the uterus, Amann found double ureters on the left side.

I have elsewhere referred in some detail, to the association of uterine cancer with other uterine, ovarian, and pelvic tumours, including dermoids.

These items show, that there is a certain connexion between developmental irregularities and cancer formation.

[1] Double uterus and vagina, cancer of left portio, two myomata of left corpus (*Cent. f. Gyn.*, 1900, No. 7).

[2] Uterus bicornis, atresia vaginæ, absence of left kidney and ureter, cancer of cervix (*Cent. f. Gyn.*, 1894, No. 18).

[3] Bifid uterus, cancer of cervix (*Lyon Méd.*, 1899, t. xc., p. 125).

[4] Uterus didelphys, cancer of one cervix (*Arch. f. path. Anat.*, 1887, Bd. cviii., S. 124).

[5] Uterus bicornis unicollis with cancer of cervix—two cases (*Mittheil. d. Vereins d. Aerzte*, etc., 1894, No. 4, p. 103).

[6] Uterus duplex, cancer of cervix (*Cent. f. Gyn.*, 1888, p. 47).

[7] Uterus bicornis, defective development of right kidney, cancer of cervix (*Deutsche Klin.*, 1860, vol. xii., p. 329).

**Sarcoma.**—In a few cases, uterine sarcomata have also been found in association with various developmental defects; thus, Howe[1] and Czerwenka have seen sarcoma concomitant with double uterus, and Briesky the same disease with "septum vaginæ retro-hymenale." Flatau, in each horn of uterus introrsum arcuatus, found a myomatous tumour, from one of which sarcomatous disease had originated. Braxton Hicks had described a case of congenital absence of the uterus, tubes, and ovaries, in which a large cystic myxo-sarcoma occupied the place of the absent uterus.

These examples suffice to show, that this form of malignant uterine disease may also be associated with gross developmental irregularity.

This concludes the evidence at present available, as to the association of the origin of uterine tumours with pre-natal developmental irregularities; but, no doubt, when attention has once been directed to this matter, additions will be made to the weighty items above adduced. However this may be, in their ensemble, these facts of themselves suffice to prove the correctness of our hypothesis.

## Mammary Tumours and Developmental Irregularity.

The ordinary anatomical description of the female mammary gland, as a flattened disc-shaped mass, is certainly very misleading. The truth is that the mamma, like the lachrymal and salivary glands, is normally a very imperfectly integrated organ, for its constituent lobules, instead of being compacted together in a small space, are generally widely diffused; moreover, in the *corpus mammæ,* its vicinity, and in the axilla, detached glandular structures are of common occurrence. It seems certain, as I have elsewhere shown,[2] that most of these redundant glandular structures are derived by sequestration from the matrix of the evolving gland, during pre-natal life. Besides these anomalies, we know from studying the embryology of the mamma, that the ducts of some of its component lobules, instead of being integrated with the majority of their congeners, are nearly always left behind when the nipple is upraised; and open about its base, rather than with them at the apex of the nipple, where they are known as the glands of Montgomery, which really are *glandulæ lactiferæ aberrantes.*

It has been shown by Schultze, Kallius and Schmidt, that—in human beings, as in polymastic animals—the first mammary rudiment presents as a linear thickening of the epidermis, which extends—on each side—from the base of the evolving anterior extremity to the inguinal region: this is the "mammary ridge," or common rudiment of the mammary glands. In human beings, spindle-shaped thickenings appear at intervals, during the second month of pre-natal life, in the course of each *milchlinie.* After a time, the connecting strands usually disappear; and only as many lenticular thickenings persist, as correspond to the number of mammæ normal in post-natal life. These linear ridges at first occupy

[1] *Boston Medical and Surgical Journal,* 1876, vol. xcv., p. 224.
[2] "Diseases of the Breast," 1894, chap. iv.

a dorsal position; but subsequently they migrate towards the ventral surface. It is easy to understand how, in the course of these modifications and migrations, portions of the matrix may be detached and left, in the axilla, or in other positions, where they subsequently give rise to aberrant glandular structures. Thus there are several ways in which mammary glandular "rests" may originate. In the axilla and its vicinity, detached glandular structures of this kind, which not unfrequently secrete milk during lactation, are by no means rare, as I have shown in my book on "Diseases of the Breast," [1] where many examples of this kind are cited.

In the *corpus mammæ* and its vicinity, similar mammary glandular *sequestra* have also been noted. "True adenoma" is the name given by some pathologists to mammary tumours, structurally exactly like a segment of the breast itself; but not in organic continuity with the mamma and its ducts. Tumours of this kind are not particularly rare; and, it is such as these, that occasionally secrete milk (so-called "milk-secreting adenoma," some galactoceles etc.). A thorough examination of this subject, in connexion with my investigations relating to supernumerary mammary sequestrations, has convinced me, that, in these cases, we have to do with overgrown mammary "rests," rather than with true neoplasms. Such is the nature of two remarkable cases of "milk-secreting adenomata," reported by Birkett; [2] of a case of "true adenoma," described by D'Arcy Power; [3] and of a milk-secreting cyst, found in a cystic sarcoma by Billroth.[4] Examples of tumour-like swellings of similar origin, in other parts of the breast and its vicinity, have been recorded by Ollier, Labbé and Coÿne, Eve, Lücke, Forbes, Cameron, and myself (from a specimen in University College Museum), as detailed in my book on "Diseases of the Breast." [5] It seems certain that the germs of these redundant mammary glandular structures, must have been detached from the matrix of the evolving gland, in early pre-natal life.

That tumours—identical in structure with mammary tumours—frequently arise from "rests" of this kind, I have clearly proved in my above-mentioned work on "Diseases of the Breast." In fact, of the mammary tumours specially examined by me *ad hoc*, I was able to determine that 14 per cent. of the fibro-adenomata, and 9·8 per cent. of the malignant epithelial tumours, thus originated; [6] as well as to indicate several instances of adeno-sarcomatous and adeno-myxomatous tumours similarly derived. This being so, it seems not unreasonable to assume, that the germs of most mammary tumours are similarly conditioned.

It accords with this, that other remarkable instances of heterotopia are also met with in the breast, and its tumours.

Thus Rindfleisch, Hacker, Astley Cooper and others, have found

[1] Chap. iv., §§ 4 and 5.
[2] Guy's Hospital Reports, 1855.
[3] Transactions of the Pathological Society, London, 1885, vol. xxxvi., p. 411.
[4] *Arch. f. path. Anat.*, Bd. xviii., S. 68.
[5] Pp. 63, 73, and 462.
[6] For recent cases of this kind, *vide* Savariaud (*Bull. et Mém. Soc. Anat.*, Paris, 1906, No. 6, p. 476); and Graham (*Journal of American Medical Association*, August 27, 1898), with references to other cases of this kind in the axilla.

cartilaginous, ossiform, calcareous, and even truly osseous structures, embedded in the otherwise normal mamma, usually in the form of localized deposits ; but Bryk, Bérard, and others, have met with diffuse calcification, sometimes in combination with true ossification.

The most feasible explanation of the presence of these anomalous formations in this situation, is that which ascribes their origin to the sequestration of sclerogenous elements from the matrix of the evolving thoracic skeleton, in early pre-natal life ; and their subsequent inclusion in the nascent mammary rudiment.

It seems certain that the various chondromatous and osteomatous tumours, primarily arising in the breast, of which Leser,[1] Hacker, Pied, Lange, Cruveilhier, Cambria, Stefanini, Astley Cooper, Nélaton, Warren, Wagner, J. Müller, Morgagni and others, have reported examples, originated from aberrant elements of this kind.

These cartilaginous and ossifying tumours, as I have previously pointed out, are especially common in the mammæ of the female dogs ; in which they are often associated with various forms of malignant disease, as well as with adenoma.

In humanity " mixed tumours " of this kind also occur ; thus, instances of malignant epithelial tumours concomitant with heterotopic cartilaginous and osseous structures, have been reported by Coen, Gross, Hacker, Warren, Heurtaux, Wagner, Busch etc. In such cases, the cancerous disease probably originated from glandular structures, displaced from their proper connexions by entanglement with skeletal sequestra : in Heurtaux's case, glandular cancer was concomitant with ossifying and chondrifying sarcoma, as was proved by the nature of the secondary growths, which reproduced the peculiarities of the primary tumour.

In mammary sarcomata similar foreign elements have been found by Arnold, Stilling, C. A. Morton, Routier, Bowlby, Pilliet, Coats, Battle, Lecène, Hueter, Durham etc. ; small calcareous concretions in these tumours have been seen by Olivier, Neugebauer, Ackermann etc. ; while, in Dubar and Clarke's cases, extensive areas of the neoplasm were calcified.

In myxomatous tumours, similar structures have been noted by Billroth, Leloir etc.

Gross and Durham, in fibro-adenomata, found similar conditions (osseous heterotopia) ; and in both these cases sarcoma subsequently supervened.

A remarkable instance of a different kind of heterotopia, has been published by Billroth : in a small round-celled sarcomatous growth removed from the breast of a girl aged sixteen, he found numerous transversly striated, spindle-shaped muscle cells. In this case, it seems probable that the foreign elements were derived by sequestration from adjacent transversely striped muscle matrix, detached during the changes incidental to mammary development, in early pre-natal life.

In like manner, dermoid cysts of the breast no doubt arise, by sequestration from the epiblastic rudiment of the evolving gland in pre-natal

[1] For details and bibliographical references to cases cited in this section, the reader is referred to my book on " Diseases of the Breast."

life, of which examples have been recorded by Rocher, D'Or, Hermann, Ribbert, Reverdin and Mayor, Van der Byl, Albers, Velpeau, Gerdy, Guyot and others. All of these were simple epidermoidal cysts, with the exception of Albers', which was also piliferous.

In several instances heterotopic epidermoidal formations, have been found comprised in fibro-cystic and fibro-adenomatous tumours (J. Griffiths, Borst, Haeckel etc.) of this part.

A similar concomitancy of dermoid cyst, with adeno-cystic sarcoma of the mamma, has been seen by J. Müller; and in cystic sarcomatous tumours of this part, Borchmeyer, B. Schmidt, Model, Grohé, Kürsteiner, Ribbert, Lecène, Wilms and others, have met with epidermoidal "rests," hornifying pearls etc.

It is to epidermoidal "rests" such as the foregoing, that we must look for the germs of the rare primary melanotic tumours of the mamma, of which examples have been studied by Cornil, Billroth, and Gurlt.

Thus for mammary, as for uterine tumours, I have shown that a considerable proportion arise from aberrant structural elements, detached from their normal connexions during pre-natal life, owing to developmental irregularity; and these tumours all bear the impress of their origin, visibly stamped in their structure. This being so, it may be inferred that even tumours in which this impress cannot be detected, nevertheless, have their origin similarly conditioned.

Moreover, there are just as good reasons for believing, that what is true for the origin of uterine and mammary tumours, is equally valid for the origin of all tumours.

# CHAPTER VIII

## THE EXPERIMENTAL STUDY OF CANCER GENESIS

It must be confessed that the results of the many attempts which have been made to produce histioid tumours experimentally—whether by implanting normal tissue elements, or those derived from tumours, or by injecting the cultures of various so-called "cancer microbes"—have, on the whole, been disappointing.

So far as malignant tumours are concerned, the results have hitherto been entirely negative, although some pathologists claim to have met with positive results, of which more anon.

### Experiments with Normal Tissue Elements.

Epidermoidal tissues are remarkable above all others for their great regenerative power, and for their tenacious vitality; while the facility with which even large pieces of skin may be transplanted, is well known to surgeons, who have practised the plastic methods of Thiersch, Reverdin, Ollier etc.

Even epidermoidal scrapings, the shavings of warts, dried bits of cuticle separated by burns,[1] the cuticle raised by blistering etc., have been successfully employed for healing ulcerated surfaces, by grafting them thereon. Recent experiments as to the limit of the vitality of the skin after its removal from the body etc., have greatly altered old ideas as to the possibilities in this direction. Thus, pieces of skin from amputated limbs have been found to retain their vitality, for thirty-six hours after their removal from the body (Brewer); and, when suitable temperature and other conditions have been maintained, for much longer periods—*e.g.*, for ninety-six hours (Marten), for several weeks (Wentscher), or even for several months (Ljunggren).

Of all the tissues of the body, the epithelial ones have, on the whole, departed less from the primordial cellular type than any others, and their constituent elements ("labile") are constantly proliferating during the whole life of the individual; hence their cells still retain their primitive powers of growth and reproduction in higher degree than any others. Thus may we account for their great regenerative power, their remarkable vital tenacity; and to this source may also be ascribed their undue proclivity to malignant and non-malignant tumour formation.

[1] Lusk found that such separated cuticle retained its vitality, and grew when grafted, even five weeks after its separation (*New York Medical Journal*, December 21, 1895, p. 799).

It has been observed of many tissue transplantations, that they have succeeded much better when pre-natal grafts were employed, than with grafts derived from the post-natal period. (Transplants of embryonic tissue in similar animals.)

With regard to epidermoidal transplantation, it is doubtful whether any such distinction is valid ; at any rate, some of the most successful results have been attained with post-natal elements.

When pieces or small fragments of epithelial tissues, derived from early pre-natal life, are transplanted or injected into adult animals, most of these grafts grow and even undergo a certain amount of differentiation, similar to what they would normally have undergone, had they retained their normal connexions ; thus, in grafts of this kind, transplanted epithelial cells have even been known to assume the glandular form etc. After a time, however, their constituent cells generally cease to grow, and are eventually absorbed. In some instances, most of the grafts degenerated from the start, such growth as subsequently supervened taking place from the surviving elements (Barfurth, Féré, Loeb, Lubarsch, Levin, Masse etc.).

In a few instances, it appears that epidermoidal cysts have resulted from experiments of this kind ; but, as to the permanence of such artificially produced new formations, there is need of further evidence. Certainly, no other kind of non-malignant epithelial tumour has ever been produced in this way ; and, above all, nothing like cancer has ever resulted.

By implanting into the peritoneal cavity of young white rats, bits of skin and parts of limbs of newly-born rats, Masse [1] succeeded in artificially producing epidermoidal-lined cysts, containing hairs, epidermoidal débris and cholesterine : such were the conditions found, when the animals were killed, two and a half months after the initial operations. In like manner he succeeded by subcutaneous grafts, in artificially producing subcutaneous "pearly" tumours.

Levin,[2] by transplanting small pieces of fœtal skin into the peritoneal cavity of rabbits, in two cases found that one or more epidermoidal "pearly" tumours resulted.

Nichols,[3] having transplanted epidermis from a fœtal rabbit, into the subcutaneous tissue of the ear of its mother, saw a "pearly" tumour form from the graft, which grew more quickly than when post-natal epidermis was used for the experiment.

Similar experiments, with post-natal epidermoidal tissues, have given almost identical results (Kaufmann, Ribbert, Schweniger etc.).

Kaufmann [4] made numerous experiments to ascertain the fate of embedded skin, employing chiefly the combs and wattles of fowls, which are very vascular tissues. Islands of surface skin were circumscribed by continuous incision ; flaps were raised on each side and united by sutures over each cutaneous island, which still maintained its normal relations with its connective-tissue substratum.

Kaufmann found that the rate of increase of the embedded epidermis

[1] *Bull. gén. de thérap. Méd. et Chir.*, 1885, t. cviii., p. 337.
[2] *Journal of Medical Research*, 1901, vol. vi., p. 145.
[3] Third Report of the Croft Cancer Committee of Harvard Medical School, 1905, p. 116.
[4] *Arch. f. path. Anat.*, Bd. xcvii., S. 236.

was greatly in excess of the normal, the grafts curling up at their margins and forming cyst-like structures, resembling the simpler kinds of dermoid cyst. This increase, in some cases, continued as long as 210 days, when a stationary condition was attained.

In connexion with the increased rate of growth here noticed, it is of interest to recall John Hunter's experiment, of transplanting the cock's spur to its comb; where it grew to a size much in excess of the normal, apparently owing to the increased vascularity of its new substratum.

Ribbert [1] cut out skin flaps, and while each was still connected with its natural basis by a narrow pedicle, it was introduced into the abdominal cavity, where each quickly adhered by its connective-tissue surface to the peritoneum, enclosing the epidermis in a cyst-like cavity. When these inclusions were examined after a sufficient lapse of time, they were found to have been converted into epidermoidal-lined cysts, with hairs growing from their walls, which contained epidermoidal débris etc.

Marnoch,[2] however, repeating experiments of this kind on guinea-pigs and rabbits, found in every case that the embedded tissue was quickly absorbed.

The possibility of the experimental production of epidermoidal cysts, and "pearly" tumours, is confirmed by the fact that tumours of this kind have often formed after certain traumata, in consequence of portions of epidermis being displaced from their normal connexions, and implanted amidst other tissues.

Most instances of this kind have been met with in the hand (especially the palmar surface of the digits) and iris; but also in other parts (vagina, cornea, thorax, thigh etc.).

These implantation cysts usually contain turbid or milky fluid, with pearly white, laminar epidermoidal tissue, within a fibrous pseudo-capsule: the polymorphic, epidermoidal cells are arranged in successive layers, the deeper ones of cubical or columnar form, merging gradually into hornified cells, as described by Polaillon (1884). In exceptional cases fragments of *cutis vera* are implanted, which may sometimes maintain a connexion with the surface skin: in the walls of such cysts, papillæ, glands, and even hairs, have been seen. Instances have also been reported in which the foreign body causing the implantation, has been found in the tumour; thus, Mr. C. A. Morton,[3] met with a thorn in the midst of the cornified, laminated matter, from a tumour of this kind in the thigh, which was known to have existed for nearly thirty years. Condon [4] has reported an example of an epidermoidal cyst of the anterior thoracic wall, secondary to fracture of the adjacent ribs. In bovine animals, piliferous subcutaneous cysts have been seen, which appeared to have resulted from skin implantations, caused by the drovers prodding the animals with the sharp goad.

The traumatic origin of implantation cysts of the iris was first indicated by Hulke (1869), who ascertained that in fifteen out of nineteen recorded cases, some form of penetrating wound had preceded the appearance of

[1] *Deutsche med. Woch.*, 1895, Nos. 1, 2, 3, and 4.
[2] *Lancet*, 1901, vol. ii., p. 6.
[3] *Bristol Medico-Chir. Journal*, 1894, vol. xii., p. 252.
[4] *Journal of Pathology*, etc., 1901, vol. vii., p. 368.

the tumours, whose epidermoidal structure he determined. The germs whence these cysts arise are displaced bits of corneal, conjunctival, or even eyelid cuticle. In several cases they have been found associated with a displaced eyelash, carried into the eye by the wounding agent. The correctness of this ætiology has been experimentally proved by Masse (1881), who caused tumours of this kind by grafting bits of conjunctiva into the iris of rabbits etc.

I have previously referred to the artificial production of uterine cysts, by the implantation of grafts of uterine mucosa.

A sensation was caused among pathologists some years ago, when Lack [1] claimed to have succeeded in experimentally producing cancer, by intra-abdominal auto-implantation in a rabbit.

Having opened the peritoneal sac and bisected each ovary, the raw surfaces of the latter were freely scraped with a sharp knife, the detached juicy and parenchymatous ovarian products being diffused throughout the peritoneal cavity. The abdominal wound was then closed, and the animal recovered. It remained well for a year, but then got thin and weak; and was killed in this condition fourteen months after the initiation of the experiment. At the post-mortem examination, the peritoneum was found studded with tumour-like formations, as well as the liver, diaphragm, mediastinum and uterus. Histologically examined, sections of these growths presented the appearance of alveolar spaces, lined by one or more layers of columnar epithelial cells. Other pathologists who have repeated this experiment, and various modifications of it, have failed to reproduce similar morbid appearances: their grafts etc., after a time, completely disappeared (Levin, Basso, Shattock, Nichols, Enderlin, Ribbert etc.).

I have previously referred to possible explanations as to Lack's success; which, in the absence of corroboration, cannot be accepted as an example of the experimental production of cancer.

It accords with this, that experiments made on other parts of the body with the same object in view, have yielded only negative results. Thus the attempts of Gilbert and Roger to produce cancer of the mamma, in old bitches, by subjecting the part to various forms of mechanical irritation, completely failed; and Cazin, by rubbing soot into irritated parts, was equally unsuccessful, although the soot particles were taken up by the local cells, as is known to be the case in that form of cancer of the scrotum called "chimney-sweep's cancer."

It was just the same with the experiments of D'Arcy Power,[2] Pierallini and Galeotti. Lately B. Fischer [3] has made fresh experiments: the tissues of the rabbit's ear having been injected with a mixture of olive oil and the fat-staining dye "Scharlach B," the cutaneous epithelium of the part was in this way separated from the subjacent tissues. Soon afterwards these epidermoidal cells showed mitoses; they thickened, ingrowing processes appeared, which penetrated the subjacent parts and even perforated the cartilage of the auricle, while epithelial pearls formed etc. In short, in all of these experiments, the histological appearances of the

[1] *Journal of Pathology*, etc., 1900, vol. vi., p. 154.
[2] *Ibid.*, 1896, vol. iii., p. 124; also 1897, vol. iv., p. 69.
[3] *Münch. med. Woch.*, 1906, Bd. liii., S. 2042.

damaged parts were very similar to those seen in malignant epithelial tumours.

Under these circumstances, it is impossible to admit the validity of the claims of Hemmeter,[1] Maniscalio,[2] Fütterer[3] etc., to have caused "adeno-carcinoma" of the stomach in various animals by irritating artificially-produced ulcers; for these claims rest solely on the local histological appearances, which in the absence of other signs of malignancy, are by no means conclusive.

Some pathologists, experimenting with tissue implantations, have reported that grafts into the ovaries grew better than those in other localities. Here Loeb's[4] interesting observations, as to the growth of epidermoidal cells in blood-serum and in agar must be recalled. In this strange environment, the epithelial cells grew and multiplied with great freedom—quite independently of any connective-tissue substratum—reproducing most of the histological appearances of epithelioma, as above detailed.

Epithelium in process of regeneration, wherever found, manifests similar changes; and Loeb[5] has specially called attention to certain resemblances between the histological appearances of epithelial healing and epithelial cancer.

Lately the interesting discovery has been made that, by treating proliferating cells with various poisons and chemical reagents (quinine, chloral, cocaine, antipyrin etc.), analogous irregularities in their mitoses and mode of growth can be artificially produced, even when quite dilute solutions are used.

It has also been shown by B. Moore that, even the reducing division, supposed to be characteristic of reproductive cells, which had hitherto only been met with—outside this sphere—in malignant tumours, can also be produced artificially, as well as other karyokinetic irregularities, by treating proliferating cells with alkaline solutions of a certain strength.

These results suggest the possibility, that the similar irregularities in the proliferation of the cells of malignant tumours, may be due to the presence of some unknown bio-chemical agency.

Here attention may be called to the fact, long well known to human pathologists, that in most chronic hyperplastic processes of epithelial-covered parts, quite analogous morphological changes commonly occur. Conditions of this kind have been specially studied by Wyss,[6] Friedländer,[7] Councilman[8] and others

Waldeyer, from the histological standpoint, having proposed for cancer the very short-sighted definition of "atypical epithelial proliferation," was soon made conscious of the serious inadequacy of such a conception, by the above-mentioned histological researches, which showed that "atypical" epithelial ingrowths were common enough, in many chronic hyperplastic processes affecting epithelial-covered surfaces.

[1] *American Journal of Medical Science*, April, 1903. [2] *Rif. Med.*, April 1, 1905.
[3] "Über die Aetiologie des Carcinoms," etc., 1903.
[4] *Journal of Medical Research*, 1902, vol. viii., p. 109.
[5] *Arch. f. Entwickelungs-mech.*, etc., 1898, vi., S. 297.
[6] *Arch. f. path. Anat.*, Bd. lxix., S. 24.
[7] "Ueber Epithelwucherung und Krebs." Strassburg, 1877.
[8] *Johns Hopkins Hospital Bulletin*, No. 2, 1890.

One of the best examples of this is furnished by the so-called "erosions" of the *portio vaginalis uteri*, wherein newly formed structures abound, very like cancer structures. These consist of ingrowths of the local epithelium, into the subjacent granulation tissue, which is thus interpenetrated by branching, anastomosing, ingrowing epithelial processes and networks. These are usually hollow, but not infrequently also quite solid cellular processes and "nests," may be formed. Thus a perfect histological counterpart of the structures commonly met with in epithelial cancer of this part may be reproduced; and yet the condition is quite innocent, for it lacks the quality of malignancy. This quasi-cancerous process is only arrested when the dense connective-tissue substratum is reached. It is thus evident, that the epithelial proliferation of cancer is not without counterparts, in various other morbid processes.

The knowledge of the foregoing facts enables us to understand how quasi-malignant tumours, comprising proliferous epithelial elements, may be caused by many various extrinsic agents, *e.g.*, traumatic, microbic, chemical etc. Thus, cases of "blastomycetic dermatitis" have been described, in which the gross and microscopical features of the lesions, were very similar to those of cutaneous cancer (Gilchrist, Stokes, Owens, Hyde, Hektoen etc.); while infectious quasi-sarcomatous tumours, similarly derived, have been met with in men and animals (Busse, Curtis, Sanfelice [1] etc.); and yet the disease is not malignant. In this category the "infective epithelioses" of Borrel may also be comprised; and I have no doubt that "Jensen's tumour" of mice, and Loeb's "adeno-sarcoma" of the neck of white rats, are of the same nature.

From a consideration of the ensemble of the foregoing items, it may be inferred that the unknown agent which causes malignant proliferation, is not specific; but rather that any kind of stimulus capable of exciting the local cells to undue proliferative activity may suffice. And, since the ontological history shows that for the requirements of physiological life, intrinsic stimuli are by far the more effective; so it is likewise probable that under pathological conditions tending to tumour formation, the same kind of stimuli prevail—such as serve as nuclear pabulum probably being in the first rank.

With regard to transplantation experiments with normal connective-tissue structures, whether of pre- or post-natal origin, the general outcome of many tentatives has been that, although at first the grafts often grew, yet, after a time, they were eventually absorbed.

In these experiments the maximum of success has been with fœtal cartilage (Zahn, Leopold, Birch-Hirschfeld and Garten).

Zahn [2] injected into the external jugular vein of rabbits, fœtal cartilage from the same animals broken up in liquor amnii; and found, when he killed and examined the dead animals a comparatively short time after the experiment, numerous cartilaginous nodules in their lungs—chiefly near the surface. Similar experiments with post-natal cartilage were entirely negative.

[1] For details of these interesting cases, *vide* Chapter X.

[2] "Sur le sort des tissues implantés dans l'organisme" (*C. R. Cong. méd. internat. de Genève*, 1878, p. 658).

Leopold,[1] continuing Zahn's line of research, made numerous experiments as to the effect of implanting fœtal rabbit's cartilage into the anterior chamber of the eye, the abdominal cavity and the external jugular vein, of rabbits. Of these the most successful were the eye implantations, some of the grafts increasing even to the extent of two or three hundred times their original size, at the same time undergoing ossification, and maintaining their vitality for considerable periods.

Helmholz [2] caused the formation of numerous small cartilaginous nodules in the rabbit's ear, by scarifying the cartilage of the same.

By injecting a mixture of finely chopped-up fowls' embryos—in normal saline solution—into dogs, Ribbert [3] claims to have produced, in a few weeks' time, malignant tumours in five out of fourteen dogs experimented on. To these claims it may be objected that the lapse of time was not sufficient, so many previous experiments having shown that the nodules which formed at first were subsequently completely absorbed.

Birch-Hirschfeld and Garten [4] injected into the liver of rabbits, hens, goats, frogs and salamanders, an emulsion of finely divided, mixed fœtal tissues, variously derived. In a few instances, cartilaginous formations were found in the liver and lungs shortly afterwards; but, they were all eventually absorbed—although, in the case of a salamander, a chondromatous formation in the liver still persisted forty-one days after the injection.

In like manner, Nichols [5] found that fœtal cartilage from a female rabbit, transplanted into the maternal subcutaneous tissue, gave rise to a considerable nodular growth, in which there was ossification.

Cohnheim and Maas [6] introduced into the jugular vein of animals, portions of the periosteum of the tibia of post-natal rabbits, dogs etc. These lodged in the lungs, where they grew for a time, producing cartilage and bone; but, by the end of the fifth week after the experiment, all traces of them had completely disappeared. Similar experiments with various fœtal tissues by Alessandri, Lwoff and Levin—and by Ribbert, Lubarsch and Levin with post-natal tissues—yielded only negative results, the grafts being invariably disintegrated and absorbed.

It was, however, long ago shown by Ollier [7] that detached flaps of periosteum implanted into the soft parts, gave rise to bone formation in their new situations; and, even the juice obtained by scraping the deep aspect of the periosteum led to bone formation, when it was implanted subcutaneously.

According to Knauer,[8] McCone,[9] Enderlin, Ribbert, and others, when entire organs—such as the ovary and thyroid—are transplanted into the same animal, or from one animal to another, they continue to survive and to perform their special functions in their new surroundings. Nichols,[10] and Basso,[11] however, found that when the whole ovary or half of it, was

[1] *Arch. f. path. Anat.*, 1881, Bd. lxxxv., S. 283.
[2] *Johns Hopkins Hospital Bulletin*, September, 1907, p. 269.
[3] "Progressive Medicine," 1905, vol. ii., p. 158.
[4] *Ziegler's Beitr. z. path. Anat.*, 1899, Bd. xxvi., S. 132.
[5] Third Report of the Harvard Croft Cancer Committee, 1905, p. 121.
[6] *Arch. f. path. Anat.*, Bd. lxx., S. 161.
[7] *Journal de la Physiologie de l'homme et des animaux*, 1859, t. ii., pp. 1, 169, and 468.
[8] *Wien klin. Woch.*, December 7, 1899.
[9] *American Journal of Obstetrics*, etc., 1899, vol. xl., p. 214.
[10] *Op. cit.* [11] *Monats. f. Geb. u. Gyn.*, Bd. xxii., Heft 5.

transplanted into the subcutaneous tissue of the same animal, these grafts—after a sufficient interval of time (up to 101 days)—were absorbed. Schultz[1] showed that ovaries transplanted into the peritoneal cavity of male guinea-pigs, dwindled in size and manifested no signs of proliferative activity, at the end of eleven days after implantation; but Hunter long ago succeeded in grafting the testicle of a cock into the belly of a hen, although experiments of this kind generally failed, and the grafted organ "seldom came to perfection."

Shattock and Seligmann, experimenting with incompletely castrated cockerels, found that where minute fragments of ruptured testis—undergoing maturation and gametogenous processes—had become grafted on the liver, intestine etc., no malignant disease ensued, notwithstanding the free production of "gametogenous" tissue in the grafts. Nichol's implantations of testicular substance into the peritoneal cavity, also gave similar negative results.

By transplanting cross sections of rabbit's and guinea-pig's uterus, into the subcutaneous tissue of the abdomen of the same animal, Nichols[2] produced cystic formations, which were in some instances multiple. The lining of these cysts resembled that of the uterine mucosa. The transplanted tissues increased and maintained their capacity for growth in most cases, as evidenced by the cellular mitoses, even for a considerable time after the experiments; but, in no case did there result a new formation having the least resemblance to myoma, or to any kind of malignant tumour.

The possibility of transplanting teeth has been well known, ever since the time of Hunter, who not only transplanted teeth, from one part of the mouth of the same individual to another part of the mouth; but also, from one human being to another; from one animal to another, and from human beings to animals. In the Royal College of Surgeons' Museum, there is a specimen showing the successful transplantation by Hunter, of a human tooth into a cock's comb.[3] The tooth grew in its new situation, and when the cock died, Hunter injected the tooth through the bloodvessels of the cock. The vitality of each part of the body, seems to have a certain autonomy. Another curious feature of transplanted teeth is, that they may transmit the poison of syphilis. Legros and Magitot have shown, that the dental bulbs may also be grafted on to the neighbouring parts—three out of sixteen experiments being successful. May not displaced bulbs of this kind be the germs of the peculiar warty growths, described by Cock, Salter and others, as sometimes being met with on the gums, and on the adjacent parts of the hard palate?

Even the extremity of the nose, ear, and the ends of fingers and toes—including a portion of the bone—have been successfully reunited after recent severance, sometimes after the lapse of several hours.

In animals, as the experiments of Bert show, the transplantation of parts between animals of the same species, can be readily effected; thus, the denuded tails and feet of rats, were successfully transplanted beneath the skin of other rats, as also detached periosteum and teeth.

[1] *Cent. f. allg. Path.*, etc., 1900, Bd. xi., S. 200.
[2] *Op. cit.*, p. 117.
[3] No. 47, Pathological Series.

In none of the foregoing experiments, except in the case of epidermoidal cyst formation, was it possible to produce experimentally anything that could be properly described as a tumour ; although Leopold's results seem to indicate, that transplanted fœtal cartilage has some tendency to evolve in this direction.

### Experiments with Papillomatous Tumours etc.

There is probably some basis for the popular belief, as to the occasional contagiousness of the ordinary cutaneous wart : thus Dr. Payne [1] relates that, after having used his thumbnail to effect the separation of warts of this kind, three similar warts developed under the nail of this thumb.

Variot [2] has succeeded in experimentally transplanting warts of this kind, from an infant to a man : the same author has also met with an instance of concomitant warts on the hands and eyelids of a child, in which it seemed probable that the disease had been transferred, from the former to the latter locality, by auto-inoculation.

Billroth [3] has noted an instance of the auto-inoculability of these warts, thus he says : "I saw a case where an ordinary wart formed on the side of a toe ; and, on the part of the neighbouring toe lying in contact with it, another wart formed."

The experiments of O. Lanz [4] are to the like effect : for, having finely chopped up some warts from the hand, he injected the product into the subcutaneous tissue of the same person ; and so succeeded in artificially producing a fresh crop. Lanz even succeeded in implanting thus a group of warts, in the form of the capital letter J, on the back of a gardener's hand. Similarly, by rubbing a healthy digit against some of these warts, the disease was implanted on the former.

As all attempts to isolate any microbe from these warts failed, Lanz concluded that the epidermoidal cells of the growth were themselves the infective agent. In a recurrent wart of the septum nasi, O'Kinealy [5] found sporozoan parasites; and Beattie has demonstrated a similar condition in cases of aural and nasal polypi.

It may, however, be inferred, from the fact that Leale [6] and others have successfully used cut-up warts, as grafts for promoting the healing of ulcerated cutaneous surfaces, without causing any wart formation, that the contagiousness of warts—to whatever agent it may be due—is easily destroyed.

It accords with this, that the contagious properties of these warts are seldom very noticeable ; and, as is well known, after a variable time, and under circumstances as yet not clearly defined, they commonly disappear "spontaneously." Here attention may be called to the not very rare occurrence of the outbreak of warts on the hand, after the making of post-mortem examinations and other similar work.

[1] *British Journal of Dermatology*, 1891, vol. iii., p. 186.
[2] *J. de Clin. et de thérap. inf.*, Paris, 1894, vol. ii., p. 529; also vol. i., 1890, p. 97.
[3] "Surgical Pathology," 1879, p. 668 (Hackley's translation).
[4] *Deutsche med. Woch.*, May 18, 1899.
[5] Proceedings of the Laryngological Society of London, 1903, vol. x.
[6] *New York Medical Record*, September 7, 1878.

Another group of papillomatous tumours, which arise from the ovary and its vicinity, manifests a higher degree of contagiousness than its cutaneous analogue. When fragments of these growths are shed into the peritoneal sac, they readily become engrafted thereon, so that very formidable-looking, diffuse masses of these warts may be thus produced. After removal of the original disease, and detachment of the more prominent secondary masses, together with irrigation and drainage, these growths generally completely disappear. Very extensive formations of this kind, may even sometimes disappear spontaneously, of which Cullingworth [1] and others have described striking examples.

The facility with which accidentally detached grafts from these tumours take root in the track of operation wounds, is well known to surgeons.

In a case of this kind, with considerable abdominal distension from intraperitoneal fluid etc., for which Cullen [2] was obliged to resort to paracentesis, papillary growths soon afterwards developed along the whole length of the trocar wound. Similar transplantation warts have often been known to form, in the scar of the operation wound in the abdominal wall; and, in fact, anywhere in the track of the operation wound. Most recurrences after ablation are no doubt of this nature.

From these clinical experiences, it is safe to predict that if warts of this kind were finely chopped up, and the product injected subcutaneously, the disease could easily be artificially transplanted in the same individual.

There is yet another common form of papilloma, which fairly often manifests contagious properties, and is transmissible to the same and to other persons; and this is the venereal condyloma. This malady is still commonly regarded as a gonorrhœal, chancrous, or syphilitic manifestation; but this is I believe a mistake.

Condylomata are not uncommonly transmitted with gonorrhœa and syphilis; but the malady is *sui generis*, and occurs independently, of which there are unmistakable instances. It is curious to find that this was also the opinion of Astley Cooper; thus, in his vivacious and interesting "Lectures on Surgery," [3] he says: "These warts were formerly considered as syphilitic, but you are to learn that they are nothing but a local disease, requiring nothing but local means for their cure. Yet, when I say local, I must observe that they frequently secrete a matter, which is able to produce a similar disease in others. I have known two instances of this. Mr. Chandler removed some warts, which were of a very large size, from a patient in the hospital; and, as he was returning the knife, his dresser put his hand forwards, and it entered just under the thumb-nail. In a little time he had an irritation about the nail, and a wart grew out of the part where the puncture had been made. It was frequently destroyed; but each time it grew again. I advised him to put on a blister, for the purpose of bringing away the nail, and then that the wart might be removed. He applied a blister, and readily removed the nail; but it also brought away the wart, which never grew again."

"The other case of warts generating themselves, was told me by a gentleman in Sussex. He was called to attend a lady in labour; he

[1] Transactions of the Obstetrical Society, London, vol. xxxiv., p. 154.
[2] "Cancer of the Uterus," 1901, p. 662. [3] P. 556.

felt something in the vagina, which appeared unintelligible, and on examination found it to be a crop of warts. He delivered her, but did not say anything about the warts to the lady. In conversation with the husband, he told him that his lady had a number of warts. The gentleman stated, that at the time he was married he had warts on the penis; and he had no doubt that he had communicated them to his wife. It is a common opinion that they are propagated by the blood, but do not entertain this idea—it is by the secretion of matter."

The nature of the *contagium* in these cases is still a moot question; but, as previously mentioned, there are reasons for believing—whatever it is—that it centres in the epidermoidal cells themselves.

It should also be noted that these warts—like their ovarian congeners—often recur after removal by surgical means. Their structure comprises, besides the papillomatous outgrowths, epidermoidal ingrowths and "nests." Yet it not unfrequently happens, after a time, that they undergo spontaneous resolution.

In this connexion, it is interesting to recall the fact, that similar contagious growths affect the genitalia of dogs and other animals; and are readily transferred from one animal to another during sexual intercourse, and by experimental implantation.

Like their human congeners, these growths after a time commonly disappear spontaneously; and such individuals are then immune to reinfection (Sticker). It is generally believed that they cannot be transplanted into any other animals except dogs; but, according to Sticker, a case is known in which a fox was successfully affected in this way.

The history of the building up of our knowledge with regard to this canine malady is very instructive, especially in that the morbid appearances on histological examination have been so diversely interpreted; thus, the malady has been described by those who have specially studied it as epithelioma, carcinoma, sarcoma, lympho-sarcoma, lymphoma, endothelioma, papilloma, granuloma, molluscoid etc.

According to Sanfelice [1] the malady is a blastomycosis; while J. J. Clarke [2] claims it as a sporozoan infection.

This shows how little the histological analysis *per se*, can be depended on for diagnosis, in doubtful cases; and it should make us very cautious about accepting as true cancer, the somewhat similar lesions met with in mice and rats.

It was Wehr [3] who first specially called attention to these tumours, by announcing that he had succeeded in experimentally producing "cancer," by implantation of the disease from the vagina and penis into the subcutaneous tissue of the abdomen of other dogs. Of twenty-six experiments, twenty-four succeeded; but, in most cases, these grafts subsequently underwent spontaneous resolution. In one case, however, the disease progressed, with the formation of secondary growths in the adjacent lymph-glands and in the spleen.

Duplay and Cazin,[4] who studied the malady in 1894, successfully

[1] *Rif. Med.*, 1904.
[2] "Protozoa and Disease," part ii., 1908.
[3] *Arch. f. klin. Chir.*, 1889, Bd. xxxix., S. 226.
[4] Transactions of the Eleventh International Medical Congress, Rome, 1894, vol. ii., p. 103.

transplanted bits of a growth from a dog's penis, into the subcutaneous tissue of other dogs. They describe the disease as infective granuloma. They also met with dissemination in one case (testis).

Geissler[1] subsequently made successful implantations; and, after one experiment, secondary growths in internal organs were found. Like Wehr, he regarded the malady as a malignant epithelial tumour.

Smith and Washbourn[2] made a very thorough study of the condition a few years later. They found that in the vagina the tumours often attained a large size, infiltrated the walls deeply, and were frequently ulcerated. In some cases secondary deposits were found in the adjacent lymph-glands, liver, and spleen. They made many succsseful transplantation experiments, but some animals were found to be immune. In several instances they witnessed spontaneous resolution, the subsidence often being concomitant with ulceration. Dogs that recovered after inoculation, were found to be immune to fresh grafts. These authors considered the disease to be, small round-celled sarcoma.

White[3] regarded the tumours as "warty growths," very different from any known form of human sarcoma; and by Sticker[4] the condition is described as lympho-sarcoma.

Seligmann[5] has lately reported other instances of this malady, which he describes as "infective tumours"; in one of these cases, the disease disseminated from the prepuce to the testis.

It is evident from the foregoing profession of faith, that pathologists still lack a really satisfactory criterion for malignancy in general, as well as for particular varieties of malignancy.

It is probable that growths of somewhat similar nature are common enough, under certain conditions, in other kinds of animals, especially in rats and mice.

Of like nature with the foregoing, are the contagious papillomata of the mouth of dogs; which, as shown by Penberthy[6] and others, spread among dogs kennelled together. This malady is also communicable by experimental implantation; and, after a time, it is apt to undergo spontaneous resolution, such animals then being immune.

The malady seems to have some similitude with the "sublingual tumour" of human nurselings, which is a papillary outgrowth, as described by Riga and Fede.

Not many implantation experiments have been reported with other kinds of non-malignant tumours; but Loeb[7] essayed the transplantation of a solid adenoma from the mamma of a rat, into other parts of the same animal and into other rats, with negative results; except that in one case, the graft into a pregnant animal increased until young were born, when it quickly dwindled away.

Lanz's[8] grafting experiments with various benign tumours, all gave

[1] "Verhandl. d. deutsche Gesellsch. f. Chir., 1895" (Twenty-fourth Congress, Berlin), S. 87.
[2] Transactions of the Pathological Society, London, 1897, vol. xlviii., p. 310.
[3] *British Medical Journal*, 1902, vol. ii., p. 176.
[4] *Zeits. f. Krebsforschung*, 1904, Bd. i., S. 418; also *ibid.*, Bd. iv., Heft 2.
[5] Transactions of the Pathological Society, London, December, 1906.
[6] *Journal of Comparative Anatomy*, 1898, vol. xi., p. 363.
[7] *Journal of Medical Research*, 1902, vol. viii., p. 74.
[8] *Op. cit.*

only negative results. Mayet,[1] however, claims to have produced sarcoma in a dog, by the injection of a filtered solution of myoma of the uterus of a woman.

It seems to me that the time has now come for clearly recognizing the fact, that there are many noxious agents, extrinsic as well as intrinsic, capable of exciting the tissue cells to proliferative activity. In the face of such evidence as I have already adduced, and of such additional evidence as I have still to supply, the dictum of Weigert—supported as it is by Ziegler and other pathologists—that irritants *ab extra* are incapable of causing formative reactions, needs modification. Borrel's researches,[2] supported as they are by many converging indications, specially point in this direction; thus he has shown, that the proliferative activity of the epithelial cells of cancerous tumours has many analogies in other morbid conditions, such as occur in molluscum contagiosum, Darier's disease, vaccinia, sheep small-pox ("la clavelée") etc., to none of which the least suspicion of malignancy attaches.

In molluscum, which is an epidermoidal new formation, many of the morphological appearances of cancer are met with, *e.g.*, irregular epithelial hyperplasia with budding ingrowths, excessive keratinization etc.; and, microscopically, various mitotic irregularities, cell inclusions etc. The contagious nature of the malady has been noted by many observers; while others have proved its transmissibility by experimental means: thus Pick inoculated some of the tumour contents into a boy and girl, and ten weeks later, characteristic tumours developed at the seats of inoculation, and subsequently others formed. No one, however, has succeeded in isolating or cultivating any causative microbe. Marx and Sticker claim to have proved that the infective agent, whatever it may be, is sufficiently minute to pass through filters which retain ordinary microbes.

It was formerly overlooked, that various noxious agents may cause the formation of quasi-malignant tumours in mankind and in animals, *e.g.*, quasi-epitheliomatous lesions due to blastomycosis, as in cases reported by Gilchirst, Owens, Hyde Hektoen etc.; and, in animals, such tumour-like new formations as are seen in coccidial disease of the rabbit's liver; and sarcoma-like tumours, due to actinomycosis and blastomycosis, such as Busse, Curtis, and others have recorded. The recollection of these conditions, will serve as a good introduction to the experimental study of malignant tumours, especially when we add thereto the remarkable instance of the infective papillomata of dogs, so often mistaken for cancer.

### Experiments with Malignant Tumours.

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During the last twenty years, an immense number of workers in this field, claim to have artificially produced malignant tumours: (1) by inoculation of cultures of various so-called "cancer microbes"; and (2) by diverse kinds of tumour-tissue grafting etc.

[1] *C. R. de l'Acad. des Sci.*, 1905.

[2] "Epithélioses infectieuses et épithéliomas," *Ann. de l'Inst. Pasteur*, 1903, xvii., p. 81.

With regard to most of these claims, supported as they are by detailed accounts of the histological analysis of the tumours, they only show how utterly unreliable such findings are, as evidence of the real nature of the malady in doubtful cases.

In dealing with these claims, the need for caution is very manifest; for, in this branch of pathological work, more perhaps than in any other, experience is apt to be deceptive and judgment difficult.

As to the first group of experiments, their history will be recorded in the sequel; [1] hence, all that need be noted here is, that their futility is now generally recognized, most of them having already passed out of recollection.

It is with the second group of claims that we now have to deal; and, at the outset, I may as well state my conviction, that none of them have scientific validity.

Most of those who have been engaged in this kind of work, have been so absorbed in their own undertakings and prepossessions, that they have seldom been able to gauge aright the scientific value of their own findings, as is abundantly testified by such review of their work as I have previously mentioned; and, as is still more emphatically confirmed, by the further examples I will now proceed to adduce.

The evidence bearing on this subject may, for convenience of discussion, be grouped under the following heads :—

(*a*) Grafting of human cancer into animals;
(*b*) Grafting cancer as between animals of the same, and
(*c*) Of different species;
(*d*) Transmissibility of cancer from one human being to another; and
(*e*) Auto-implantation.

### (*a*) *Grafting Human Malignant Tumours into Animals etc.*

Of the numerous attempts that have been made from time to time, to transmit human malignant tumours experimentally to animals—whether by grafting, inoculating with the juice, magma etc., by intravenous injection, and other ingenious methods—the results have almost invariably been negative.

Among the earlier experimenters, only Langenbeck,[2] Follin,[3] C. O. Weber,[4] and Goujon,[5] claim each a single successful result.

Langenbeck injected the creamy juice of a recently removed malignant tumour of the human humerus, mixed with defibrinated blood, into the femoral vein of a dog. The injection induced intense dyspnœa, which soon subsided; so that a week later, the animal seemed in fairly good health. Subsequently emaciation set in, and the animal was killed in this state, sixty-three days after the injection. The post-mortem examination revealed several small, hard nodules, varying in size from

[1] *Q.v.* Chapter X.
[2] "Schmidt's Yahrbücher d. gesam. Med.," 1840, Bd. xxv., S. 104.
[3] Lebert's "Traité pratique des maladies cancéreuses," 1851, p. 136.
[4] "Chirurgische Erfahrungen und Untersuchungen," Berlin, 1859, S. 289.
[5] *Thèse de Paris*, 1866: "Exposé de quelques faits tendant à démontrer que les cancers de l'homme," etc.

an almond to a lentil, at the surface of each lung; and a similar small nodule in the middle of the left lung. Histologically examined, these nodules resembled in structure the tumour of the humerus, whence the juice used for injection was derived.

Follin repeated Langenbeck's experiment by injecting into the jugular vein of a dog, a magma derived from a recurrent cancerous mass, recently removed from the axilla of a woman, whose breast had been previously extirpated for cancer. On the fourteenth day after the injection, the dog was killed; and, on examining the body, several small firm nodules were found in the lungs, in the walls of the heart, and in the liver. These formations were seldom larger than a pin's head; and, histologically, they were found to comprise "cancer cells."

The nodules in these cases, were probably nothing but consolidating inflammatory lesions, around embolic tumour grafts artificially produced by the intravenous injections. Had more time been allowed, they would probably have completely disappeared. Such was actually the course of events, in the many similar experiments, subsequently made by Virchow, Vogel, Wyss, Billroth, and others. In these cases, the animals experimented on were not killed until several months after the injection; when no trace of cancer nodules could be found in any part of their anatomy.

The positive results of the other experimenters, are even less convincing than the foregoing.

Dupuytren [1] fed dogs and other animals for considerable periods with human malignant tumours, but they did not acquire the disease; and the dogs that Alibert caused to swallow discharge from cancerous ulcers etc., experienced similar immunity. Shattock and Ballance [2] have, in like manner, fed white rats for several months, with fresh cancers of the female breast, with only negative results.

In comparatively recent times, several additional examples of this kind of experiment have been reported; but, almost invariably, the results have been negative; thus of the numerous attempts made by Sticker [3] and Hemmeter,[4] to implant human cancer into dogs, cats, guinea-pigs etc., all were unsuccessful.

In judging the value of the alleged positive results, it is necessary to bear in mind that quasi-malignant tumours of parasitic origin—to which, as we now know, humanity is liable—may have been used, some of which are known to be inoculable: for instance, the quasi-sarcomatous tumour of the thigh, described by Curtis [5]—which was due to blastomycetic infection—was easily inoculated into various animals; and it is the same with the still commoner quasi-malignant tumours due to actinomycosis (as shown by the experiments of Wolff and Israël), tuberculosis, and other infective parasitic pseudo-plasms.

Subjoined are some examples, of the more notable of these alleged positive transplantation experiments.

Into the peritoneal cavity of a white rat, Dagonet [6] injected a *mélange*

[1] *Gaz. Méd. de Paris*, 1838, p. 47. [2] *British Medical Journal*, 1891, vol. i., p. 567.
[3] *Zeits. f. Krebsforschung.*, 1904, S. 413.
[4] *American Journal of Medical Science*, April, 1903.
[5] *Ann. de l'Inst. Pasteur*, 1896, t. x., p. 449.
[6] *Arch. de Méd. Exp.*, etc., May, 1904.

of a cancerous lymph-gland, secondary to epidermoidal cancer of the penis, in saline solution. After some months, the animal began to emaciate progressively; and died thus, fifteen months after inoculation. Multiple nodules were then found in the omentum, spleen, and liver, which were of similar structure to the original human tumour. Considering the great proclivity of white rats, kept in captivity, to develop quasi-malignant tumours spontaneously, or by contagion from other rats, of which more anon, it seems likely that this is the explanation of the tumours found in this case, especially as the peritoneum was free from the disease. The very numerous experiments of this kind, that have been made by other observers, with only negative results, also point to this conclusion.

By injecting the ascitic fluid derived from a patient with colloid cancer of the peritoneum, into the jugular vein of a guinea-pig, Gaylord [1] found—when the animal was killed three and a half weeks after the injection—a small nodule in one lung, which he considered to be "adeno-carcinoma." Subsequently numerous other experiments of this kind were made, with a similar result in a few cases. In a dog thus treated, he found—when the animal was killed ninety days after the injection—numerous "cancerous" nodules in the liver. Subsequently Hansemann histologically examined the pulmonary nodule, but could find no evidence of its cancerous nature. In one of the above cases, the ascitic fluid was kept for two weeks in an incubator, before it was used for injecting into the jugular vein of a guinea-pig; when this animal was killed, fifty days later, nodules of "beginning cancer" were found in its lungs.

Having collected the ascitic fluid from a patient with colloid cancer of the peritoneum, and kept it for ten days in an incubator, Pease [2] practised intravenous injection of this fluid into guinea-pigs; and, in one case, when the animal was killed three and a half weeks later, he found a nodule of "adeno-carcinoma" in the lung.

Lewin [3] claims to have transmitted human ovarian cancer to dogs; while Dagonet and Mauclaire [4] also claim to have transplanted human rectal cancer into rats.

Many unsuccessful attempts have been made to produce leukæmia experimentally; but Löwitt [5] now claims to have succeeded, by intravenous injection of material from leukæmic organs into rabbits.

By implanting into rabbits, guinea-pigs, and dogs, various human cancer tissues, Bosc and Vedel [6] claim to have produced "cancerous" nodules at the seats of inoculation.

Herzog [7] has many times tried to produce malignant epithelial and connective-tissue tumours, in rabbits and guinea-pigs, by injecting triturated human material subcutaneously, intra-peritoneally, and into the anterior chamber of the eye, but without success; for, although in some cases nodules formed at first, they subsequently completely disappeared.

[1] *American Journal of Medical Science*, 1901, vol. cxxi., p. 503.
[2] "Public Health Papers and Reports," vol. xxv., 1900.
[3] *Zeits. f. Krebsforschung.*, 1906, Bd. iv., S. 55.
[4] *Arch. de Méd. Exp.*, 1904, t. xvi., p. 552.
[5] "Twentieth Century Practice of Medicine," 1903, vol. xxi. (suppl.), p. 571.
[6] *La Semaine Méd.*, 1898, p. 166.
[7] *Journal of Medical Research*, 1902, vol. viii., p. 74.

Juergens[1] injected into the peritoneal cavity of rabbits, a magma derived from a metastatic sarcoma of the human cerebral meninges. Three months later, one of the animals was found to have a tumour in its right eye. On post-mortem examination a month later, a sarcomatous tumour, the size of a hazel nut, was found there. The tumour teemed with coccidia-like organisms. This is probably a case of microbic infection.

In another rabbit, in which bits of a myxo-sarcoma of the human ovary, had been implanted in the peritoneal cavity, tumours were found—when it was killed some months later—in the lungs, small and large intestines. These tumours also teemed with coccidia-like bodies.

Juergens also claims to have successfully implanted into animals fragments of sarcoma, taken from a human subject three days after death.

Some interesting implantation experiments have been made with human melanotic tumours.

These were started many years ago by Goujon,[2] who injected substances of this kind into various animals. At the seat of inoculation, he noted that one or more small black tumours sometimes formed. Soon afterwards pigment appeared in the adjacent glands; and, at a subsequent period, in more remote glands. He specially notes the great augmentation of the total amount of pigment which ensued after the injection, as if by multiplication of living pigment-producing elements.

By injecting triturated human melanotic tumour in saline solution, into the spleen of a guinea-pig, O. Lanz[3] found, seven weeks later, a small pigmented nodule in the animal's left external ear; moreover, all the internal organs contained a large amount of free and intra-cellular pigment, *i.e.*, there was diffuse melanosis.

Bosc and Vedel[4] inoculated guinea-pigs with human melanotic sarcoma material, subcutaneously and intra-peritoneally; and so produced in them nodules of melanotic sarcoma.

By implanting a small fragment of a secondary melanotic sarcoma from a woman, at the root of the tail of a mouse, Pfeiffer[5] produced a melanotic tumour at the seat of implantation. He transplanted fragments of this tumour into twelve other mice, in one of which a similar growth developed. Even before Goujon's time Klencke (1843) claimed to have successfully transplanted human melanoma into horses and dogs.

Juergens[6] had previously made many experiments of this kind; thus, having implanted under the conjunctiva of a rabbit's eye, a small bit of recently extirpated human melanoma, a fortnight later a melanotic tumour had developed at the seat of implantation.

Juergens also implanted, in the peritoneal cavity of six rabbits, fragments of melanoma from the human pancreas, with the result that within a few weeks, each of these animals developed intra-abdominal pigmented tumours, with similar nodules in the pericardium and heart as well, in one case.

All these new formations teemed with pigmentiferous coccidia-like bodies.

1 *Berlin klin. Woch.*, No. 15, 1895, p. 331; see also pp. 465 and 747.
2 "Inoculabilité des éléments pigmentaires ou mélaniques," *Gaz. des Hôpitaux*, 1867, p. 339.
3 *Deutsche med. Woch.*, May 18, 1899. 4 *Op. cit.*
5 "Die Protozoön als Krankheitserriger," Jena, 1891, p. 204. 6 *Op. cit.*

In this connexion it is interesting to recall, that Lancéreux found the blood of patients affected with disseminated melanotic tumours, very rich in pigment-bearing elements.

Here also reference may be made to the little-known facts about melano-mycosis,[1] and its experimental transmissibility; as well as to the recent experiments of Charrin and Le Play,[2] who by subcutaneous and intra-peritoneal injection into various animals, of pure cultures of the fungus (*Stearophora radicicola*), which grows on the root of the vine, produced black-coloured tumours like melanomata. Bard[3] also has shown the parasitic nature of certain melanotic tumours.

Fischel's attempts to implant human melano-sarcoma into rats all failed; and a similar fate befell Roux and Metchnikoff's implantations of the same morbid substance into the chimpanzee.[4]

With material obtained by harpooning fragments of human cancers and mashing them up, Dubois[5] inoculated animals subcutaneously. As a result, tumour-like swellings formed soon afterwards, in several cases.

Boinet[6] inoculated a series of forty rats intra-peritoneally with fresh human malignant tumours; and, a month later, one of these animals became paraplegic, and died thus a few days afterwards. It was then found to have two cancerous tumours adherent to the spine, above the central tendinous part of the diaphragm, the adjacent dorsal vertebræ and liver being invaded, and the spinal cord compressed. Histological examination of these nodules showed that they comprised proliferating epithelial elements, similar to those of the human tumour, whence the material used for inoculation was originally derived.

The other results of this series of experiments were negative; as also were numerous subcutaneous implantations in various animals.

Mayet[7] claims to have successfully transmitted human cancer to white rats, under circumstances which preclude the possibility of tissue or cell grafts being concerned in the process. Thus, by repeated subcutaneous injections of a glycerine extract of aseptically macerated human cancer, filtered through porcelain or asbestos, he has several times produced in these animals, after an interval of some months, "des lésions cancéreuses épithéliales." It is of interest to remark that with dogs and rabbits, similar experiments yielded only negative results.

Firket[8] implanted fragments of human sarcoma into rats; and, five weeks later, in several cases, tumours developed at the seats of inoculation.

By injections of cancer juice from human malignant tumours into white mice, Francotte and De Rechter[9] claim to have caused the formation of cancerous tumours, some months later, at the seats of inoculation.

As we have already seen, white mice and rats are so prone to originate quasi-cancerous tumours spontaneously, that the causative relation of the injections to the tumours in these cases, is by no means evident.

Among those who have essayed to transplant human cancer to

[1] Transactions of the Pathological Society, London, vol. xlii., 1891, p. 423 (Delépine).
[2] *C. R. de l'Acad. des Sci.*, 1905.
[3] *Lyon Méd.*, 1885, t. xlviii., p. 407.
[4] *Bull. de l'Acad. de Méd.*, 1903, p. 3.
[5] *Bulletin Méd.*, August 16, 1896.
[6] *La Semaine Méd.*, June 13, 1894.
[7] *Lyon Méd.*, 1905, p. 1356; also *ibid.*, December 11, 1904, and August 19, 1893.
[8] *La Semaine Méd.*, 1893, p. 8.
[9] *Bull. R. Acad. de Méd. de Belgique*, 1892, p. 999.

various animals, with negative results, mention may be made of Duplay and Cazin, Shattock and Ballance, Senn, Weigert, D'Arcy Power, Senger, Fischel, Wickham, Klebs, D'Anna etc.

Shattock and Ballance[1] undertook many experiments to this end, implanting portions of quite fresh human malignant tumours into monkeys, dogs, rats, cats, and sheep; but the results were always negative; hence they concluded that it is impossible to transmit the human disease to animals.

In two of their experiments, entire scirrhous cancers of the female breast were inserted into the abdominal cavity of animals, and disappeared after a time without leaving a trace; in like manner, large slices of chondrifying round-celled sarcoma of the humerus—when similarly treated—completely disappeared.

Having in view the immense preponderance of negative results and the many sources of fallacy, to some of which I have previously referred—I can only regard the alleged successes in this kind of experiment, as resting on insufficient evidence to ensure credibility.

(*b*) *Grafting Experiments as between Animals of the Same Species.*

It seems reasonable to suppose that implantation experiments might have a better chance of success, if confined to animals of the same species; but, in this direction also, most experiments have proved abortive (Bert, Jeannel, Gratia, Senn, Köster, Erbre, Doultrelepont, and many others).

In comparatively recent times, however, several experimenters allege that they have succeeded in transmitting "cancer" from mouse to mouse, and from rat to rat. What is the real nature of this so-called cancer?

The great mistake of those who have so prematurely identified "Jensen's mouse tumour" with cancer is, that in making their diagnosis they have placed far too much reliance on histological appearances—the fallaciousness of which has so often been demonstrated in recent times—and far too little on the ensemble of the indications available for diagnostic purposes.

It was by following this line of fallacies that Wehr, Smith and Washbourn, and others, formerly persuaded themselves and the majority of pathologists, that the infective venereal tumours of dogs were examples of contagious inoculable cancer; indeed, it is only lately that this widespread fallacy has been exploded.

Experimental pathologists are only now beginning to recognize, although pathological anatomists have long been aware of it, that epithelial proliferations—in their structural details very like cancer—are of common occurrence in many non-cancerous conditions.

These considerations alone should have sufficed to cause the present subject to be approached with the greatest caution, but the event has been far otherwise; for, the modern experimenter being a law to himself, is only too often quite impervious to the plainest lessons of history, even to those that may be learnt from his own speciality. This narrowness of outlook, is the cause of the extraordinary concatenation of blunders with

[1] Proceedings of the Royal Society, London, 1890, vol. xlviii.

which the history of the experimental study of cancer is cumbered; indeed, if we put aside the Münchausen creations, very little solid fact remains as the outcome of so much vapouring.

Now, what are the plain facts in respect to which "Jensen's tumour" differs *in toto* from cancer, or any form of human malignant tumour? They are briefly these:—

The disease is highly contagious; and the observations of many competent pathologists (Gaylord, Borrel, Haaland etc.), who have specially studied this aspect of the malady show, that when infected animals are introduced into cages with healthy animals, the latter take the malady as if by local contagion.

There can be no doubt that mice kept in captivity, especially those confined for experimental use in scientific laboratories, which are often numerous and get but little hygienic attention, are singularly prone to epidemic outbreaks of "cancer," as signalized by Gaylord and Clowes,[1] Haaland,[2] Borrel,[3] Loeb [4] etc.

As long ago as 1891, Morau [5] found that mice fed with a paste composed of chopped-up tumour and bread-crumbs, developed the disease; and some recent observations of Borrel, as to the spread of the infection through contaminated water, are of similar import.

Because his experience of this occurrence has been negative, so far as evidence of contagion is concerned, Dr. Bashford [6] seems to think that this negative experience justifies him in denying point-blank the very positive results of the above-mentioned pathologists, which he ascribes to fallacious observations, erroneous deductions, and lack of personal experience. In my opinion this criticism is unjustifiable, and without scientific warrant. It is not the first mistake of this kind that Bashford has made; for, having denied, as the result of his own negative experience, the positive results of Clowes,[7] as to the immunity of mice—whose tumours had undergone spontaneous cure—to reinoculation, he has recently had to eat his own words; and, so long as this vicious kind of criticism is indulged, similar results may be anticipated.

That various parasites to which mice are specially prone, such as sporozoa, are capable of originating contagious quasi-malignant growths, we know from the researches of Borrel and others. Yet these "infective epithelioses" are just as different from cancer, as are the coccidial tumours of the rabbit's liver, with which they are really analogous.

As Twort [8] has lately indicated, many cases of so-called "cancer" in mice, are commonly associated with invasion of the part by sarco-sporidia (Miescher's cylinders); while the extraordinary facility with which this sporozoan muscle parasite can be transmitted from mouse to mouse, by feeding with contaminated muscle, has been well demonstrated by T. Smith.[9]

[1] *British Medical Journal*, 1906, vol. ii., p. 1555; also *Journal of the American Medical Association*, 1907, p. 15.
[2] *Ann. de l'Inst. Pasteur*, 1905, vol. xix., No. 3, p. 156.
[3] *C. R. Soc. de Biologie de Paris*, 1905, p. 770.
[4] *Univ. Penn. Med. Bull.*, U.S., April, 1907.
[5] *C. R. Soc. de Biologie de Paris*, 1891, t. iii., pp. 289, 721, and 801.
[6] *Lancet*, 1907, vol. i., p. 802.
[7] *British Medical Journal*, 1906, vol. ii., p. 1548.
[8] Transactions of the Pathological Society, London, 1907.
[9] *Journal of Experimental Medicine*, May, 1905, p. 429.

Some recent observations by Borrel[1] seem to show that certain of these "Jensen tumours" are formed round vermiform parasites, which end their existence thus, after having lived for a time in the animal's blood; and the experiments of Rouget have shown that mice and rats are very prone to trypanosome infection.

In this connexion, it is also of interest to note, that Borrel, Gaylord and Calkins have often found the blood of these tumours teeming with parasitic spirochætæ.

In the present state of this inquiry, it would be premature to speculate as to the precise value of these significant finds; but they seem to point to distinct causative agents for these pseudo-plasms.

Since this was written Jacobs and Geets, by inoculating mice and rats with cultures of Doyen's *Micrococcus neoformans*, claim to have produced thus similar local and general cancerous tumours.

By exposing pieces of "Jensen's tumour" to the very low temperatures generated by liquid air, Moore and Walker[2] lately found that these tumours nevertheless retained their power of inoculability. It is well known that many microbes and spores retain their vitality even after exposure to such low temperatures, which kill the tissue cells. From this it may be inferred, that the infective agent in these tumours is of parasitic origin.

There is no evidence as to the occurrence of contagion, such as is met with in these mice pseudo-plasms, in any form of human cancer—at least, not outside the Münchausen sphere; but, in the contagious venereal malady of dogs, analogous conditions are commonly met with. "Jensen's tumour" is readily transmissible by implantation to other mice, the proportion of successful experiments often being as high as 50 per cent.; indeed, Morau—using only closely related animals—succeeded in 80 per cent. of his experiments.

No such property is ever manifested by human cancer; but, with the contagious venereal pseudo-plasm of dogs, similar conditions obtain.

A considerable proportion of white mice are immune to the contagion of this disease, whether in its spontaneous or experimentally determined form; and sometimes whole families manifest this peculiarity. The same phenomena have often been noted in the contagious malady of dogs.

Moreover, "Jensen's tumour" fairly often undergoes spontaneous resolution; and the cured animals are then immune to further contagion, giving only negative results when inoculated, as Gaylord and Clowes have specially pointed out. With human malignant tumours, no such spontaneous curability has ever been scientifically demonstrated; but, with the venereal pseudo-plasms of dogs, this phenomenon is of common occurrence.

"Jensen's tumour" is circumscribed and easily enucleable, the tissues of the host forming no part of it; moreover, the latter do not acquire cancerous properties, nor do they become interpenetrated by processes of the pseudo-plasm; and, besides this, "Jensen's tumour" generally causes no cachexia.

[1] *C. R. Soc. de Biologie de Paris*, 1905, p. 770; also *British Medical Journal*, 1906, vol. ii., p. 392.

[2] *Lancet*, 1908, vol. i., p. 226.

Finally, according to Apolant and Ehrlich,[1] "Jensen's tumour" in the course of experimental transmission often changes its anatomical type—from the epithelial to the sarcomatous etc.; and Morau found, under similar circumstances, that its physiological type also changed, with corresponding alteration in its power of inoculability. Lately from "adeno-carcinomata," inoculable "sarcomata," and "sarco-carcinomata" of mixed type, have been obtained; and these latter have again produced "pure sarcomata"; while these malignant formations have been found to revert to "benign adenoma."

In all of these vitally important respects, which, taken together, are crucial for diagnostic purposes, "Jensen's tumour"—whatever its real nature may eventually turn out to be—is totally unlike any form of human cancer.

On the other hand, like the venereal malady of dogs, "Jensen's tumour" can usually be successfully grafted into other animals of similar species.

Another feature in regard to which the two maladies present a certain resemblance is, that in both secondary disseminative lesions occasionally result; so that, in this respect, "Jensen's tumour" resembles certain artificially produced pseudo-plasms—such, for instance, as those Sanfelice, O. Schmidt, Curtis, Busse, and others produced, by inoculating animals with certain pathogenic yeasts.[2]

X It was Morau,[3] in 1891, who first specially directed attention to this so-called cancer ("epithéliôme cylindrique") in mice; and subjected the malady to experimental tests.

The original tumour developed spontaneously in the subcutaneous tissue of the axilla of a captive white mouse. It was easily enucleable, non-adherent to contiguous structures, and caused no disturbance of the animal's general health. A portion of this tumour, immediately after its aseptic ablation, was by trituration reduced to a magma, which was forthwith injected into the subcutaneous tissue of a series of other white mice. About three months afterwards, it was noticed that nearly all the injected animals presented similar tumours at the seats of inoculation and elsewhere, which subsequently slowly increased in size. One of these tumours was then enucleated, and from it fresh magma was prepared, with which another series of mice was injected; and these also, after a similar interval, acquired the disease. Experiments of this kind were successfully continued through several generations.

It is noticeable that the animals used for these experiments were all of the same strain, closely inter-related, and had all lived in the same cages. This no doubt explains the very large proportion—over 80 per cent.—of successful implantations; for, when animals of foreign strains were used, the proportion of successful inoculations was much less. In subsequent experiments of this kind, Morau found that when the malady had been artificially transmitted through a considerable number of generations, the inoculability of the tumour markedly diminished.

[1] *Berlin. klin. Woch.*, 1905, xlii., S. 871; *ibid.*, 1906, No. 2; also Arbeit. aus k. Inst. f. exp. Therap. z. Frankfurt-a.-M., 1906, S. 65 and 77.

[2] For details, *vide* Chapter X.

[3] *C. R. Soc. de Biologie*, Paris, 1891, t. iii., pp. 289, 721, and 801; also *Arch. de Méd. exp.*, etc., September, 1894, t. vi., p. 677.

Morau seldom noticed dissemination, except after traumatism X affecting the edge of the tumour.

No cultures could be obtained from any of the many tumours examined, nor could any microbes be discriminated.

Attempts to transplant the malady into other animals than mice failed.

Jensen[1] did little more than repeat, extend and popularize Morau's experiments, which in the intervening decennium had been forgotten. From a small subcutaneous tumour on the back of a white mouse, whose histological structure resembled that of tubular cancer, he took pieces and brayed them in a mortar with physiological salt solution. Small quantities of this *mélange* were injected subcutaneously into a series of white mice, with the result that tumours, like the original, developed at the seat of inoculation in most cases. Even by the fourteenth day after injection, small nodules were visible ; and, in the course of some months, quite large tumours had formed—sometimes as large as, or even larger than, the affected mouse. The tumours were transmitted in this way through over twenty generations of mice, about half of those inoculated producing tumours. Some animals, and even entire families, were immune ; and those in whom first injections failed, yielded negative results to further injections.

From white mice the disease was only occasionally and with difficulty transmitted to the grey kind ; and negative results followed all attempts to produce it experimentally in white rats, guinea-pigs, rabbits, goats and ducks.

Jensen regarded his experimentally produced tumours as implantation grafts, derivatives of the transplanted tumour cells ; and he could neither detect any microbes in the tumours, nor get any cultures of such. Metastatic tumours were not noticed.

Borrel[2] performed many similar experiments with like results. In tumours of some duration, he found metastases very common, especially in the lungs. These he determined arose from graft-like cellular emboli, detached from the primary tumour, which reached the lungs by the bloodvessels. He demonstrated many tumour grafts of their kind, within the pulmonary bloodvessels.

Haaland[3] and Bashford[4] have also made many confirmatory experiments of this kind ; but without otherwise adding to our knowledge of the malady, the real nature of which has yet to be determined.

In a communication published subsequently to the one above cited, Borrel[5] has reported some interesting particulars as to these tumours. In the centre of each nodule he has commonly found marked indications of active phagocytic processes, characterized by the presence of large mono-nucleated cells, greatly hypertrophied, vacuolated, and "*bourrées de détritus de toute sorte.*" In the vicinity thus characterized, numerous large blood sinuses abounded. Around the central area the epithelial tubules, which constituted the real tumour, were disposed in a radiating manner. These phagocytic areas, he considers due to small vermiform parasites,

[1] *Hospitalstidente*, No. 19, 1902; also Nos. 21 and 22, 1903: and *Zent. f. Bakt.*, 1903, Bd. xxxiv., Nos. 1 and 2.

[2] *Ann. de l'Inst. Pasteur*, 1903, vol. xvii., p. 81. [3] *Ibid.*, 1905, vol. xix., p. 156.

[4] Scientic Reports of Cancer Research Fund, 1904 and 1905.

[5] *C. R. Soc. de Biologie de Paris*, 1905, t. i., p. 770.

which end their existence here after having lived for a time in the animal's blood; and in this connexion it is interesting to note, that he has often found spirochætæ in the blood sinuses of these tumours, sometimes in immense numbers, as also has Ehrlich.

Loeb,[1] like Apolant and Ehrlich, also claims to have artificially produced carcinomatous and sarcomatous tumours in Japanese mice, by inoculating them with carcinomatous growth, derived from the submaxillary gland of a Japanese mouse.

Like mice, rats are also subject to a quasi-malignant kind of tumour, which is contagious, transmissible by implantation, and in other respects much resembles the above-described malady of mice.

Hanau[2] was the first to describe and experiment with this pseudoplasm. He injected material from an "epidermoidal cancer" of the vulva of a rat, into the tunica vaginalis testis of two other rats: one of these died seven weeks later, with diffuse nodular "cancer" of the peritoneum; the other was killed eight weeks after inoculation, when two "cancerous" nodules were found, one in the adrenal, the other in the gubernaculum testis. With material from one of these nodules, a third rat was injected; and when it was killed, three months afterwards, it presented a tumour at the seat of injection, as well as diffuse nodular growths throughout the peritoneum, and in the posterior mediastinum. All of these tumours were histologically of similar structure to the original vulvar tumour. Hanau considered that these results show, "successful grafting of tumour tissue."

Eiselsberg[3] grafted portions of a "fibro-spindle-celled sarcoma" from the back of one rat, into the peritoneal cavity of two other rats: in one of these a large pseudo-sarcomatous tumour of the peritoneum developed, of which the animal died, five months after the implantation. In its histological structure, this latter tumour resembled the original.

Velich[4] transplanted portions of a "periosteal sarcoma" of the femur of a white rat, into series of other rats, through nine generations; and, at the seat of implantation, a tumour generally formed, which structurally resembled the original tumour. In one instance he succeeded in thus transplanting a tumour fragment, twenty-four hours after its removal. After several generations of successful transplantations, the power of the grafts to grow underwent great diminution, or was altogether lost. Uninoculated rats kept in the same cage with their inoculated congeners, developed similar tumours. Disseminative tumours were not seen in any of these inoculated animals. Injections with tumour juice, from which the cells had been removed by filtration, gave only negative results.

Loeb,[5] with material derived from an "adeno-cystic sarcoma" from the thyroid region of a white rat, made a series of transplantations into other white rats—chiefly into the subcutaneous tissue, and into the peritoneal cavity; and, in most cases, at the seat of implantation, a tumour similar in structure to the original resulted. Local disseminative

[1] *Penn. Univ. Med. Bulletin*, July, 1906, p. 113.
[2] *Corresp. Bl. f. schw. Aerzte*, 1889, No. 11, S. 334.
[3] *Wien. klin. Woch.*, 1890, No. 43, S. 927.
[4] *Wien. med. Blätter*, 1898, Nos. 45 and 46.
[5] *Journal of Medical Research*, 1902, vol. viii., p. 46; also *ibid.*, vol. vi., p. 28.

nodules were often seen, as well as contact implantation, and even distant dissemination. In one case, after excision, the disease recurred locally, with dissemination in distant parts. In a few cases he succeeded in producing similar pseudo-plasms, by injecting the fluid contents of the tumour cysts, which contained cellular elements; but, after these had been removed by filtration, the injections were always negative. In a fair number of cases the rats used proved to be quite immune. Several experiments were made to determine how long, after removal, the grafts would maintain their inoculability; and, by keeping them on ice, they were found to be effective even after five days' exposure.

Attempts to implant the disease into white mice, guinea-pigs, rabbits, and other animals, all failed; but, in two cases, he succeeded in transmitting it into a hybrid of a white and grey rat.

In no case could any microbes be detected in the tumours; hence, Loeb concluded, that the latter were derived from the transplanted cells.

Herzog[1] got similar results in a series of over fifty implantations, comprising eight generations. Fluid extracted from these tumours, and made cell- and microbe-free by special filtration, when injected never gave a positive result. Attempts to implant the malady into rabbits all failed.

Flexner and Jobling[2] have also successfully implanted mixed-celled sarcoma of the vesicula seminalis of a white rat, into other white and grey rats, with the formation of metastases in several cases.

Loeb queries: "Are these growths sarcomata or granulomata?" and he decides for the former; but to me it seems, for reasons previously mentioned, that the ensemble of this malady, like the similar affection of mice, is totally unlike any known form of human malignant tumour.

A few other examples of the alleged successful outcome of this kind of implantation still remain to be mentioned.

Thus, in the course of attempts to transmit cancer from dog to dog, Mathis,[3] after many failures, claims a single success.

In this case, having injected material from "thyroid cancer" of the dog, into the same part of another healthy dog, a tumour developed at the seat of injection; which, in the course of three months, attained the size of a pigeon's egg. Histologically this tumour resembled the original one.

In like manner, Arloing and Tripier[4] succeeded in transplanting a graft of mammary "cancer" from one dog to another; and Novinsky[5] grafted bits of an epithelial alveolar tumour from the nose of one dog, into the subcutaneous tissue of another dog—the grafts growing into tumours like the original, in two out of forty-two implantations. Lately Bashford[6] has reported similar results.

Goujon,[7] having grafted epithelial cancer from one guinea-pig into another, maintains that the latter presented at the seat of implantation an almond-sized tumour, together with cancerous nodules in the viscera, when it was killed fifteen days after the operation.

[1] *Journal of Medical Research*, 1902, vol. viii., p. 74.
[2] *Cent. f. allgem. Path. u. path. Anat.*, April 15, 1907.
[3] *Rev. des Maladies Cancéreuses*, October, 1896, p. 16.
[4] *Lyon Méd.*, May 26, 1895, p. 119.
[5] *Cent. f. med. Wiss.*, 1876.
[6] *British Medical Journal*, 1906, vol. ii., p. 1554.
[7] *Op. cit.*

### (c) *Grafting Experiments as between Animals of Different Species etc.*

Notwithstanding alleged instances to the contrary, the transmission of cancer from one animal to another of a different species, has never been definitely proved.

Doultrelepont[1] failed to transplant grafts of cancer from the mamma of a bitch into guinea-pigs and rabbits; and most experimenters have failed to transmit the so-called "cancer" of mice and rats to other animals of different species.

I have previously referred to the negative results of Dupuytren's and Shattock's experiments, of feeding dogs and other animals with human malignant tumours.

Here passing mention may be made of certain alleged examples of the transmission of cancer from human beings to animals, or *vice versâ*, by accidental contagion: for instance, Hyatt has reported the transfer of melanotic sarcoma from the horse to man; Gross that of cancer from domestic animals to man; Kuhn the case of a woman, who inoculated her finger with cancer while tending a cancerous cow; Juergens the transfer of epithelioma from a fowl to a man's finger; Budd the case of a pet dog, who contracted cancer of the tongue, from licking his master's cancerous lip; Bosc, the transfer of epithelioma from a trout—that had been eaten raw—to a young man's tongue, wounded at the time by the spines of the fish etc.

According to Noël, even certain tree tumours ("arboreal cancers"), may by contagion communicate the malady to human beings and animals; while Behla considers that the cabbage parasite (*Plasmodiophora brassicæ*) is equally potent in the same direction.

Wasps, bugs, fleas, and flies, have all been regarded as infective agents in this sense; and Behla considers that the peculiar local distribution of cancer at Luckau, is due to the agency of contagion conveyed by dogs, cats, rats, mice etc., besides the uncooked cabbages, radishes, water-cresses with other vegetables, and the dirty water.

I have mentioned these items, not that any present credibility attaches to them, so far as I can see; but because they ought to be in the naturalist's mind, when considering this aspect of the subject.

### (d) *The Transmission of Cancer as between Human Beings.*

If cancer could be proved to be an inoculable contagious malady, the question as to its causation would be greatly simplified, in favour of extrinsic factors; but, so far as we have hitherto examined this question, no reliable evidence of contagion has been forthcoming.

Interest, of course, centres especially as to the evidence of contagiousness between human beings; and this is the aspect of the question to which I now propose to invite attention.

Even as far back as the middle of the seventeenth century, there were those who believed that cancer was communicable by direct con-

[1] *Arch. f. path. Anat.*, 1869, Bd. xlv., S. 501.

tagion ; and, in support of this belief, the case of a woman with ulcerated cancer of the breast, who is said to have communicated the disease to her three sons who slept with her, is instanced by Zacutus Lusitanus (1649). A later author of this period, Nicolaus Tulpius (1672), in support of the same thesis, has related the case of an elderly lady with ulcerated cancer of the breast, who is also said to have communicated the malady to her servant and nurse. Even as late as the middle of the eighteenth century, cancer patients were refused admission into the Hôtel Dieu at Reims, on account of the supposed contagiousness of the malady.

In opposition to these fanciful conceptions, I can appeal to my eight years' experience at the Middlesex Hospital, where—although I was daily in the cancer wards—I never noticed a single fact that could possibly be construed as evidence of the communicability of malignant disease from one human being to another ; but I noticed many indications which seemed clearly to imply, that the disease was neither infectious nor contagious. At that time, the special wards were packed with patients in advanced stages of cancer, mostly of the breast and uterus, in a state of ulceration. There were no day-rooms for these patients ; they lived and died in the same wards. No sooner was one dead, than her place was taken by another. The crowding was great ; yet, during a period of twenty years, not a single instance is known in which a nursing sister, probationer, nurse, ward-servant, surgeon, student, or anyone engaged in attendance on the cancer patients, ever acquired the disease. The nursing-sister in charge held her office for over a quarter of a century, but she was never affected.

Among these cancer patients were many who had been inadvertently admitted, with various chronic ulcerative affections of a non-cancerous nature ; some of these lived for years in the cancer wards, but none of them ever took the disease.

Many supposed examples of the transmission of cancer from one human being to another have from time to time been recorded (Budd,[1] Guelliot,[2] Bosc,[3] Guermonprez,[4] Cabot,[5] Fabre,[6] Behla,[7] Boas,[8] MacEwen,[9] and others) ; but, the evidence adduced as to contagion in these cases, is of such a flimsy and obviously unreliable nature, as to absolve me from the necessity of detailed refutation.

On the other hand, besides such items as I have previously mentioned, there is some strong evidence as to the non-contagiousness of the disease between human beings, which I will now proceed to relate.

The attempts made in Paris at the Hôpital St. Louis, early in the nineteenth century, by Alibert,[10] Biett, and others, to inoculate them-

[1] For a series of cases, *vide* the *Lancet*, 1887, vol. ii., pp. 727, 888, 919, 986, 1091, 1145, etc. I regard these simply as highly exceptional coincidences.

[2] *Gaz. des Hôpitaux*, 1892, No. 129, p. 1209 ; also *L'Union méd. du Nord-Est*, 1891, xv., p. 106 *et seq.*

[3] "Le Cancer," Paris, 1898.

[4] *Bull. Méd.*, March 11, 1896.

[5] *Boston Medical and Surgical Journal*, 1901, vol. cxliv., p. 471.

[6] *Thèsede Lyon*, 1892.

[7] *Deutsche med. Woch.*, June 27, 1901.

[8] *Verhandl. d. XVIII. Cong. f. Méd.*, 1900, S. 374.

[9] *Glasgow Medical Journal*, 1886.

[10] "Description des Maladies de la Peau observées à l'Hôpital St. Louis," 1806, p. 118.

selves and their pupils with the disease, were uniformly unsuccessful. In modern times, Senn [1] implanted the fresh pulp of a recently removed cancerous gland into the subcutaneous tissue of his forearm, with a negative result; and, in like manner, ended Wickham's attempt to inoculate himself with tissue from a case of "Paget's disease" of the breast, associated with cancer.

Notwithstanding the frequency with which surgeons and medical men are exposed to contagion, in the ordinary course of their professional duties, not a single well-authenticated instance has been recorded, in which the disease has been acquired in this way.

Of the thousands of persons habitually engaged in attendance upon the victims of this disease, how few have ever been similarly affected!

The United States Census Report, for 1900,[2] having shown a high death-rate from cancer, among nurses and midwives, as compared with occupied females in general, the attempt has been made to utilize this item, as evidence of contagion; but, besides the need for caution in dealing with the statistics of this country owing to their peculiar mode of collection etc., as mentioned in a previous chapter, which make these data particularly unsuitable for determining a question of this kind, it is also necessary to notice the great disparity in age distribution, which is alone sufficient to entirely account for the diversity in cancer proclivity, the majority of nurses and midwives being very much older than most domestic servants, who constitute the largest class of employed females; besides, the total number of deaths from all causes (1,330) in this class, and of cancer deaths (98), is much too small to enable reliable death-rates to be calculated. In short, these sources of fallacy render this item, quite worthless as evidence of cancer contagion, even if it could otherwise be properly employed for such a purpose.

In matters of this kind, naturally occurring experiments are often far more conclusive, than those made under artificial conditions, with their numerous sources of fallacy. "Sadly strange as it may seem," says Matthews Duncan, "there is scarcely any disease, however formidable or however loathsome, in spite of which sexual intercourse and conception may not take place." This is strikingly true of uterine cancer, which is far more frequently complicated with pregnancy than is generally believed and, in the earlier stages of the disease, no doubt the sexual appetite is increased, and sexual intercourse is of common occurrence.

In proof of this, it may be mentioned that Noble [3] had no difficulty in collecting records of 166 cases of pregnancy complicated with uterine cancer, published during the decennium 1886-1895; and it would be easy to add to this list. Cohnstein [4] has reported a remarkable series of cases, in which more than a single pregnancy was known to have taken place, during the course of uterine cancer. I know of instances of pregnancy having occurred after amputation of the cancerous cervix, and after curettage for the same.

[1] *Journal of the American Medical Association*, April 28, 1906, p. 1255.
[2] Vol. iii., part i., p. ccxcviii, etc.
[3] *American Journal of Obstetrics*, etc., February, 1896, p. 283.
[4] *Arch. f. Gyn.*, Bd. v., S. 366.

Yet, in spite of these facts, I am not aware of a single well-authenticated case of cancer of the penis acquired in this way.

Of 134 men with cancer of the penis, tabulated by Demarquay,[1] only one had a wife with uterine cancer. Bossi,[2] who has recently reinvestigated this important subject, has arrived at a similar result: of 180 husbands known to have had marital relations with wives the subjects of uterine cancer, not a single one had acquired the disease.

In like manner, Bayle—many years ago—reported that, having had under observation a considerable number of men, who had habitually maintained marital relations with wives known to be affected with uterine cancer, not one ever contracted the disease.

The comparatively few cases, in which cancer of the uterus and penis have coexisted in husband and wife is so small, as to deprive them of all value as evidence of contagion. It accords with this, that cancer of the penis is a rare affection, while uterine cancer is exceedingly common; thus, in 1900, 3,679 women died of uterine cancer in England and Wales; but, only 100 men died of cancer of the penis.

Among the forty-three cases of this conjunction collected by Behla and Guelliot from various sources, is one reported by Tross, in which the penile disease is said to have consisted of structures identical with those of the uterine malady—glandular cancer of the cervix. Referring to this case, Dr. Brand[3] says: "It alone is sufficient to prove that transference of cancer cells occurred—that cancer is therefore contagious." When such supreme importance is attached to a particular case, it surely is not too much to ask, that all the details relating thereto shall be publicly set forth, and submitted for verification, to the scrutiny of some competent professional tribunal; in the absence of any such details and impartial scrutiny, I shall perhaps be pardoned if I decline to accept the interpretation of the histological appearances in the sense alleged.

Again, the children of cancerous mothers do not acquire the disease, even when the placenta, uterus, or other part of the genital tract is the seat of the malady. Moreover, mothers with cancer of the breast have often suckled their infants with the diseased organ, without transmitting the malady to their offspring.

Thus, there is every reason to believe that cancer cannot be transmitted from one human being to another; and that it is, in fact, essentially a non-contagious malady.

### (e) *Auto-Implantation.*

Several instances of the apparently successful auto-implantation of malignant tumours, in human beings, have now been reported.

Hahn,[4] for instance, having removed some small cancerous nodules from the skin of a woman with recurrent mammary cancer, implanted them into small wounds made in the skin of the mammary region, on the opposite side of the body. In the course of two months, these grafts

[1] "Mal. Chir. du Pénis," 1876.
[2] *Gaz. degli Osped.*, April 13, 1902.
[3] *Quarterly Medical Journal*, May, 1903.
[4] *Berlin. klin. Woch.*, 1888, No. 21, S. 413.

increased to the size of peas; and, when the patient died with general metastases some weeks later, they were as large as cherries—their histological structure resembling that of the primary breast tumour.

Cornil[1] has reported two similar cases. In one of these a fragment of cancer (*épithéliôme tubulé*), taken from the recently removed breast of a woman, was implanted into the opposite breast; where, in the course of several weeks, it grew into a small tumour. In the other case, a fibro-spindle-celled sarcoma having been removed from the female breast, a fragment of this tumour was implanted into the opposite breast; where, in the course of two months, it attained the size of an almond. The implanted tumour was then excised; and, histologically examined, it proved to be of the same structure as the original.

At least two other surgeons are said to have repeated these experiments, with similar results.

If we accept this evidence as conclusive, what has been accomplished amounts to the artificial production of metastasis.

In a somewhat similar experiment by Senn,[2] in which a fragment cut out from a cutaneous cancer of a man's leg, was inserted into another part of the same leg, no growth subsequently ensued; and, by the end of a month, all traces of the graft had completely disappeared.

I have found very few experiments on record, as to the auto-implantation of cancer in the lower animals: Senn's[3] attempts on a dog, affected with sarcoma of the lower jaw, failed; but, with the so-called "cancer" of rats and mice, successful auto-implantations have been made.

Some weighty items of evidence as to the auto-inoculability of cancer come from clinical sources.

In a considerable number of cases it has been observed, that when cancerous growths have remained for some time in contact with eroded, epithelial-covered surfaces, the latter have at length become cancerous, as if by direct implantation.

Cripps[4] has related the case of a woman, with extensive cancerous ulceration of the left mammary region; who, being unable to put on any dress, had kept her arm—bent at a right angle—in constant contact with the disease for several months. In consequence of this, the skin in the vicinity of the elbow became the seat of a cancerous ulcer, several inches in diameter.

A somewhat similar case has been previously recorded by De Morgan.[5] He says, "My colleague, Mr. Shaw, attended a woman whose pendulous breast—the seat at its most dependent part of ulcerated cancer—rubbed against the skin of the thorax. At the point of contact, a circular patch of cancerous ulceration (the size of a florin) took place, the intervening skin between this and the fold of the mamma remaining healthy."

A. Williams,[6] in a woman aged sixty, has reported the spread by

[1] *Bull. de l'Acad. de Méd.*, 1891, No. 25; also *Le Progrès Méd.*, 1888, Nos. 21 and 27.
[2] "Surgical Bacteriology," 1889, p. 262.
[3] *Op. cit.*, p. 261.
[4] Transactions of the Pathological Society, London, 1881, vol. xxxii., p. 111.
[5] "On the Origin of Cancer," London, 1872.
[6] *British Medical Journal*, 1887, vol. ii., p. 1369.

"contact infection," of an ulcerating cutaneous epithelioma of the inner part of one thigh, to the corresponding part of the opposite thigh.

Examples of the spread of cancer by "contact implantation," from the uterus to the vagina, have been related by Thorn,[1] Czempin,[2] Fischer,[3] Russell,[4] and others.

One of Thorn's patients, a multipara aged forty-six—whose uterus had been deflected to the right, where it had become fixed in its faulty position by adhesions—subsequently developed cancerous "cauliflower excrescence" of the portio. Owing to the faulty position of the uterus, the diseased portio was constantly in contact with the left side of the vagina, at a considerable distance from the fornix. In this position papillary cancer developed, which fitted the similar growth on the portio, "like a saucepan-lid." Elsewhere the vagina was free from disease.

Niebergall, Winter, Pfannenstiel and Leopold have described cases, in which the primary outbreak of the disease in the corpus uteri, had been followed by the appearance of similar disease in the cervix ; which they ascribe to inoculation, by contact with the primary cancerous polyp, or with débris given off from it.

In like manner, instances have been noted by Hamburger,[5] Walter and others, of the spread of cancer from one vulva to the other, both the tumours being of the same histological structure.

In various other parts of the body, facts of similar import have been reported, *e.g.*, from one lip to another (Bergmann), from one vocal cord to another, from one eyelid to another (Vennemann), from the tongue to the adjacent cheek (Lücke), from the visceral to the parietal pleura, and likewise from the visceral to the parietal peritoneum etc.

I have seen several examples of this kind, especially in the mouth and bladder.

Klebs[6] has met with instances in which cancer of one part of the alimentary tract, has been followed by the development of cancerous nodules of similar structure at other parts lower down, as if by the implantation there of detached fragments ; *e.g.*, (*a*) ulcerated epithelioma of the œsophagus, with two small nodules of similar structure below the cardia ; (*b*) ulcerated epithelioma of the mouth, with a tumour of similar structure in the large curvature of the stomach ; (*c*) epithelioma of the dorsum of the tongue, with a similar tumour in the large curvature of the stomach.

Fütterer[7] has lately published another case of this kind, and refers to six others.

Moxon[8] and Ebse[9] have described the spread of the disease from the trachea to the lungs, in a similar way ; while Dickinson saw numerous discrete growths form in the peritoneum, in consequence of the rupture of a cancerous lumbar gland, which shed numerous detached particles.

[1] *Cent. f. Gyn.*, No. 10, 1894.
[2] *Zeits. f. Geb. u. Gyn.*, Bd. xvi., Heft 1.
[3] *Cent. f. Gyn.*, 1891, S. 549.
[4] *American Journal of Obstetrics*, etc., vol. i., p. 293.
[5] *Med.-chir. Rundschau*, 1892, No. 12.
[6] *Handb. d. path. Anat.*, Bd. i., S. 190.
[7] *Medicine*, 1902, vol. viii., p. 177.
[8] Transactions of the Pathological Society, London, vol. xx., p. 18.
[9] *Cent. f. Chir.*, 1884, No. 48 (cited by Kraske).

into the peritoneal cavity. Schenk has seen perforated gastric cancer spread in this way to the ovaries and uterus.

Another important class of cases, in which implantation plays a leading part, comprises what I am in the habit of calling post-operative cancers.

Thus, Courtin,[1] Reinecke[2] and others, have noted the frequency with which, after tapping for ascites due to cancerous disease, the wound track itself became cancerous; as if through implantation in it of cancerous elements, conveyed there by the ascitic fluid.

Nicaise has also seen sarcoma supervene in the track of a punctured wound, made through the abdominal wall, into a uterine sarcoma, under the supposition that it was a cyst.

After the extirpation of malignant tumours, the resulting wound may not infrequently be grafted with the disease in this way; thus Schopf[3] reports that, having had to make lateral incisions into the vagina and vulva, during the course of vaginal hysterectomy for cancer of the uterus, these incisions subsequently became cancerous, as if from contact infection. Leopold and others have had similar experiences.

In other parts of the body the same thing has often been noted; thus, Lawrie[4] has described a case in which, during exploratory laparotomy for cancer of the sigmoid colon, he removed a ruptured cancerous gland, with his fingers; fourteen months later a cancerous nodule appeared in the upper part of the laparotomy scar, owing to some fragment of the cancerous gland having been implanted there during extraction.[5]

The by no means rare occurrence of this kind of accident, after supravaginal amputation of the cancerous uterus by the abdominal route, and after many abdominal operations, is, I think, now beginning to be generally recognized.

Indeed, there are good reasons for believing, that eroded surfaces may be infected through contact even with the discharge from cancerous ulcers etc.; and many surgeons now admit the traumatic dissemination of the disease, through the inoculation of wounds by the escape of "cancer juice" during operations.

Hence, care should be taken to avoid cutting into malignant neoplasms during their removal; for, such is the great tenacity of life and the wonderful proliferative power, of even the most diminutive fragments of cancer, that when left behind they only too often constitute fresh centres of disease.

In view of such considerations as the foregoing, even the extraordinary examples of auto-inoculation reported by Schimmelbusch and Kaufmann, cannot be summarily dismissed as being altogether improbable: the former states that a man who was in the habit of handling his cancerous ear, transmitted the disease to his lip, through the medium of his finger-nails; while the latter relates the case of a man with epithelioma of the hand, who conveyed the disease to his eyelid, by continuously rubbing the part with the diseased hand.

[1] *C. R.* 7me., *Cong. de Chir. Française*, 1895.
[2] *Arch. f. path. Anat.*, 1870, Bd. li., S. 391.
[3] *Wien. med. Woch.*, 1891, No. 45.
[4] *British Medical Journal*, 1906, vol. i., p. 198.
[5] For other instances of this kind *vide ibid.*, 1907, vol. ii., p. 255 (Butlin); and *Lancet*, 1907, vol. ii., p. 1311 (Ryall).

## CHAPTER IX

## CANCER AND TUMOUR GROWTH IN RELATION TO GROWTH IN GENERAL

THE genesis of tumour germs, and their growth, are problems that require separate consideration.

In a previous chapter, comparing tumour germs with ova, I insisted, with reference to their origin, that just as cells embedded in the stroma of an ovarium become ova by excessive growth at the expense of adjacent nutritive materials, which they divert from other cells; so it may be inferred that those cells which originate tumours, become different from their congeners in a similar way.

It will, I think, aid us in arriving at correct ideas as to the nature and conditions of tumour growth, if we extend our analogy, so as to embrace also this part of the problem; that is to say, by comparing tumour growth with the growth from the ovum—for no doubt all the attributes of tumours are but the consequences of their modes of growth.

### Of Growth in General.

But, before entering on this matter, it seems desirable briefly to survey the subject of growth in general.

At the outset it must be mentioned, that growth is always accompanied by marked changes of form; and, moreover, for each kind of being and for each part, growth has a determinate limit. With regard to the various parts and organs, their growth in the course of ontogeny is by no means uniform; for, while in some the process ceases, in others it is renewed with fresh vigour. Indeed, the ontogeny of every higher organism presents a twofold progress, proceeding *pari passu*. On the one hand, there is continuous perfecting of bodily structure by increasing histological and morphological differentiation, whence the various tissues and organs result; and, on the other hand, there is continual transition from lower and more general, to higher and more specific types of organization.

The most remarkable of these morphological manifestations of growth take place in young animals, especially during the embryonic period; but, changes of this kind also occur in post-natal life, even in mankind and the highest animals, of which examples are seen in dentition, puberty, pregnancy, lactation etc.

The earliest products of the histological differentiation of the embryonic epiblast and hypoblast, are layers of the epithelial cells which function as the primitive organs. The organs of the adult are evolved from these layers by further differentiations: certain of their cells become as it were the germs, whence these organs bud forth in a definite and orderly manner, the essence of the process being that at certain points more intense cell proliferation sets in than elsewhere. Solid bud-like processes of proliferous cells thus arise; which, as they increase, grow into the adjacent tissues. The further development of such a bud or initial cellular mass may be either continuous or discontinuous: it may spread as ingrowth, outgrowth, or sometimes as both, the ultimate form of the resulting organ being only gradually attained through subsequent successive modifications.

In these various types of normal epithelial new formations, we see the prototypes of corresponding pathological new formations. In all cases, these morbid productions seem to result from a modified, super-induced repetition of some portion of the normal developmental process of the affected part or its vicinity. Just as there are good reasons for believing that the primordial starting-point of every organ is a single cell; so, likewise, we may conclude that every tumour probably has a similar origin. This need excite no surprise, when we recollect the wonderful reproductive properties of cells.

Under normal conditions, growth proceeds in a regular and orderly manner, in accordance with the specific hereditary tendency of the whole; and, just as the great problem of physiology is to explain this orderly sequence, so the great problem of tumour pathology is to explain how, under abnormal conditions, the disordered rhythm of growth is produced of which tumours are the outcome.

### Of Growth in Cells.

Ever since the establishment of the cell theory, it has become clearer and even clearer, that the solution of all biological problems—including those of tumour formation—must ultimately be sought in cell life and cell processes. We will therefore proceed with our task by studying growth in the individual cell. As the one really essential, universal, physiological property common to all living things, growth is a phenomenon of the greatest importance. To our senses cell growth manifests itself as a rhythmic process, in which increase of size alternates with increase of number or multiplication; and, at the same time, there is concomitant structural differentiation of the growing unit, that is to say, change from the general to the special. This change is commonly termed "development," and is often held to be fundamentally distinct from growth. It may be said that growth is due to the tendency of like units to unite, and of unlike units to separate; or, as Spencer has it: "Growth is an integration with the organism of such environing materials, as are of like nature with it." All living things grow by taking into their substance new particles, which they dissolve and convert into new living matter. This latter, the physical basis of life, is the nitrogenous carbon compound—protoplasm; of which it may be said, that its molecules are of such kinds and so compounded, as easily to admit of rearrangement. Thus, its constitution specially fits it to receive and produce the internal changes, required to balance the external changes, the continuous adjustment of which—according to Spencer—constitutes life.

The young cell is small; it increases in size, through the assimilation by its elements of a larger quantity of nutritive materials, than is required for the repair of waste and maintenance (anabolism). Having thus attained a certain normal size, which varies for different kinds of cells, this excess of nutritive materials is dissipated and used up for the production of new cells (katabolism); that is to say, there is reproduction, multiplication, or growth of the cell beyond its individual limit of size.

As to the real nature of the force which determines the limit of cell growth and its form, we can only surmise that it has some similitude to crystal formation. Just as, in the latter, we see that the whole aggregate exerts a force, which constrains the newly integrated units to take up a certain definite form; so, it may be assumed, the rearrangements of organic units are determined in a somewhat similar way. This hypothetical property, as to the real nature of which we are in both cases ignorant, is called polarity. Thus regarded, polarity may be defined as the resultant of the physico-chemical forces which determine molecular arrangement; hence, in the evolution of organic form, the polarity of protoplasm is a very important factor.

It is also noteworthy, that the size and qualities of particular cells depend chiefly upon heredity, that is to say, upon inherent potentialities of parental origin.

In every act of reproduction, a certain quantity of protoplasm is transferred from the producing to the produced cell; and, along with it, the molecular motion peculiar to the parental unit. The phenomena of heredity are, in fact, dependent upon this material continuity and partial identity, of the producing and produced organisms.

It is generally believed that each cell, after its formation, begins at first to grow slowly, then reaches its greatest rapidity of growth; and ultimately growth declines, until at last it ceases: thus, there is a wave-like rhythm, with periods of increase, maturity and decline. According to Minot,[1] however, the rate and power of growth steadily decrease, from the beginning to the end of life. If we accept this view, it follows that stoppage of growth is not due to the attainment of maturity, but is merely the final term of a long series of losses; and, pushing this argument to its logical conclusion, Minot maintains that loss of vital force—"senescence"—is the stimulus which inaugurates discontinuous growth or proliferation.

In these ways then the form and substance of cells are altered, and at the same time their physiological properties are altered, so that new relations are established.

All sorts and conditions of growth in the end, will be found to depend upon the molecular processes of nutrition—understanding by this term the whole of the material changes wrought in the organism, through the

[1] "Reference Handbook of the Medical Sciences," 1889, vol. iii., p. 398.

influence of the surrounding outer world. These many complicated conditions never being absolutely identical for any two cells, it follows that variability is a universal property of all cells. Thus, change of nutrition is unquestionably the true cause of all morphological variation ; which, according to Virchow, always has its foundation in a pathological accident. By disease, in fact, we merely imply a phase of life, whose manifestations deviate in some way from the normal, owing to perturbations caused by changed or abnormal conditions of existence. Thus, our conception of disease is a purely physiological conception, which recognizes the identity of the laws governing physiological and pathological processes ; and traces the diversity between the two, to differences in the conditions under which the organic forces and substances operate. A necessary outcome of this conception of disease is, that every pathological process has its physiological prototype—a great principle of modern pathology the full significance of which is, even now, far from being adequately recognized.

In any given case, it is impossible to say where health ends and disease begins ; thus, no one can determine where what are called normal morphological variations end, and where cancer and tumour formations begin. All that we can say is, that when structural or functional changes are hurtful, they belong to the province of pathology. The study of healthy processes must, therefore, necessarily precede that of the study of the phenomena of disease.

Had the pathologists of half a century ago, been imbued with more adequate knowledge and understanding of the fundamental principles and methods of biology, our present knowledge of tumour pathogenesis would be much in advance of the standard actually attained ; for, even now, it is chiefly owing to this kind of defect, that so many modern endeavours miscarry.

Other things being equal, growth varies according to the surplus of nutrition over expenditure ; and it is unlimited or has a definite limit, according as this surplus does or does not progressingly decrease.

Why should growth tend in the direction of cell proliferation, rather than to the production of large unicellular aggregates ? We must seek the answer to this question, in the conditions of molecular cohesion in protoplasm. In all cases the process is evidently one of disintegration ; and, as such, opposed to that integration which constitutes the individual. According to C. F. Wolff, there is a certain relation between the commencement of the process and declining growth. For cell multiplication does not take place while the parental individual is growing rapidly, that is to say, while the process of growth greatly exceeds the opposing forces ; but it begins, when nutrition is nearly equalled by expenditure.

It is customary to speak of both protoplasm and nucleus, as the essential constituents of a typical cell ; and to these modern cytologists add the centrosome. It must, however, be distinctly understood, that all the parts of the cell are knit together in organic unity. Most cytologists now regard the nucleus as the most important constituent of the cell ; and, to this organ, they specially attribute its maintenance and multiplication as a living entity. Thus, the nucleus presides over the constructive metabolism of the cell, being specially concerned in the formative processes involved in all kinds of physiological and pathological growth and development; and, it is through the nucleus, that specific qualities are transmitted from cell to cell, by heredity. The earliest manifestations of all kinds of cell growth and multiplication are, therefore, to be looked for in nuclear changes. Young cells generally have relatively large nuclei, surrounded by scanty protoplasm.

In support of these claims for nuclear pre-eminence, it may be mentioned that Grüber, Nussbaum and others, have shown that when unicellular organisms are artificially divided, only those fragments which comprise nuclear elements, are capable of growing and multiplying—the others gradually perish.[1]

The centrosome is a minute body, or pair of bodies, which lies in the cytoplasm near the nucleus, surrounded by the rounded attraction sphere (archoplasm), or by a cytoplasmic radiating aster. It is regarded by Boveri and other cytologists as the special organ of proliferation; and, therefore, the dynamic centre of the cell. The precise status of the centrosome is, however, still *sub judice.*

Growth being an integration with the organism of such environing matters as are of like nature with it, is necessarily dependent upon the available supply of such materials: of these the most essential is water, for it is certain that living things cannot grow without it, however abundant the other requisites may be. Light, heat, and nutriment are also important factors. The quality and quantity of nutritive material at the disposal of a cell, has a profound influence upon its behaviour.

In cell proliferation, to which all organic units are inherently prone, the occurrence and nature of the process—whether by agamogenesis, gamogenesis, or alternation of generations—is determined by the conditions of nutrition. Impregnation may be regarded, as merely one of the various conditions, which affect the process: the influence of the male element on the germ-cell, as Caspar Friedrich Wolff long ago suggested, being comparable to that of a kind of nutriment.

There are good reasons for believing that, in unicellular forms, life runs in cycles of asexual cell divisions, which are strictly limited—the separate cells of one such cycle being collectively analogous to the entire body of a multicellular organism. Each of these cycles begins and ends with an act of conjugation. In support of this conclusion, Maupas' researches on infusorians may be instanced. By following for a long period the life-history of various species, through the entire cycle of their existence, he showed that after a time the processes of growth and development in these unicellular animals, tended to come to an end, owing to "senescence"; and this defect could only be overcome by conjugation. Thus, having isolated an infusorian, which in the course of several months produced agamically 215 generations, Maupas found that the individual cells were exhausted; and, the return to their normal standard of vitality could only be effected, after conjugation with an alien strain. In the

[1] It has, however, recently been demonstrated by Boveri and Delage, that denucleated eggs of the sea-urchin can be fertilized, when they give rise to normal gastrulæ and larvæ; so that, if these experiments are substantiated, the nucleus is not the sole vehicle of heredity.

absence of this union, the race died out. Thus conjugation was shown to be requisite, for restoring to the cells their exhausted vitality—union of the nuclei of the conjugating cells being an essential part of the process. In this way, the physical admixture of protoplasmic matter from two different sources, is ensured. The new cell thus produced must be regarded as an entirely new formation, since in it the characters of both the conjugating cells are potential.

Many biologists have proved that abundant nutrition favours asexual proliferation: thus Zacharias found that planarians multiplied rapidly in this way, when copiously supplied with food; but, when the latter was withheld or greatly reduced, asexual multiplication ceased. In like manner Maupas, having restricted infusorians to vegetarian diet, noted great diminution in the rate of the asexual cell divisions.

### Growth in Multicellular Organisms.

Just as the constituent elements of single cells, together with their various differentiated parts, *e.g.*, nucleus, centrosome, etc., are knit together into an organic unity; so, in like manner, the constituent cells of the multicellular organism, are also integrated and co-ordinated into one organic whole, notwithstanding the structural and functional differentiations of their constituent cells. In such organisms, the tissue cells can only be regarded, in a restricted sense, as being independent units; for their autonomy is subservient, in greater or lesser degree, to the requirements of the whole aggregate.

There can, I think, be no doubt that the activities of the local cells are largely controlled by the totality of the forces which determine the form of the whole organism; and the best conception as to the nature of this force that biologists have yet evolved, appears to me to be the one formulated by Spencer, which represents it as being akin to the force which determines the integration of crystals. The tissue cells must thus be regarded as local centres of a formative power, pervading the growing mass of the whole aggregate. If, during the later stages of development, some cells acquire a disproportionately high degree of physiological independence, this may be regarded as a secondary consequence of development, by virtue of which these cells become more or less emancipated from the general control.

The researches of Carnoy and other cytologists give some warrant for this conception; for, they have demonstrated that the constituent cells of multicellular organisms, are knit together by protoplasmic cell-bridges (*ponts intercellulaires*), in which cell membrane, protoplasm, and sometimes even nuclear filaments, are involved (Ide). Hence it may be inferred, that besides serving as nutritive channels, these bridges also transmit physiological impulses from cell to cell.

In view of these discoveries, it seems probable that Heitzmann was not far from the right track, when he described the metazoan organism as a kind of huge protoplasmic syncytium, of which the constituent cells are merely nodal points.

It is generally admitted that the growth of multicellular organisms depends chiefly upon the multiplication of cells, and only to a slight degree upon the increase in size of individual cells ; hence, it seems clear, that the amount of growth is determined by limitation of the process by which cells are increased, both as regards number and rate of multiplication.

The question of the causative factors of cell growth and multiplication, is the most fundamental and important in the whole range of biology—physiological as well as pathological—and, in the proper understanding of this question, the mystery of cancer and tumour formation undoubtedly concentres.

Biologists have long been aware of the fact, that the unfertilized ova of many animals are capable of a certain amount of developmental exegesis ; although, after a time, the process usually ceases spontaneously, and the cells degenerate and are absorbed.

In certain exceptional cases, however, the ontological exegesis of the egg may proceed to its destination without fertilization ; and, whether the development is by gamogenesis or by agamogenesis, seems often to depend chiefly upon the conditions of nutrition.

In this connexion the phenomena of parthenogenesis are of much interest, as representing a transition from sexual to asexual reproduction. Here germ-cells, which often appear to be formed exactly like ova, develop into new individuals, without the influence of any fructifying sperm. It occurs in certain plants and animals, and is probably of the nature of a relapse from the sexual method.

Among our common honey-bees, male individuals arise only from unfertilized eggs by parthenogenesis ; while the fertilized eggs originate females exclusively, which evolve into fertile forms (queens), or sterile forms (workers), according to the nature of their food. Moreover, it appears probable, that the very same egg may develop agamically ; which, under other circumstances, would have been fertilized. These considerations show, that there is no such fundamental distinction between gamogenesis and agamogenesis, as is commonly supposed.

In true parthenogenesis there occurs along with gamogenesis, in a true ovarium or homologous organ, a form of agamogenesis exactly like gamogenesis, save in the absence of fertilization, as in silkworm moths. False parthenogenesis occurs when new individuals arise from buds in pseud-ovaria, which are not ova properly so called, as in *Aphides.*

This process is intermediate between true parthenogenesis and that form of agamogenesis called by Owen *metagenesis*, in which new individuals *bud out*, not from any specialized organs ; but from *unspecialized* parts of the parent, which are generally external, but may be internal, as in *distoma.*

Herein we have evidence that the reproductive properties of somatic and of germ cells are the same in kind ; and that they differ only in degree.

We now pass to the very remarkable series of events known as the *alternation of generations.* Until comparatively recently, it was believed that in every species the successive generations were always alike—

*homogenesis*; but it is now known that this is not always the case—*heterogenesis*.

Many plants and animals produce a generation unlike their parents; these may produce others like themselves, or like their parents, or like neither, and so on; but eventually the original form reappears. Here gamogenesis alternates with agamogenesis or parthenogenesis.

In further illustration of this subject, reference may be made to the life-history of the plant lice (*Aphides*), which has been admirably worked out by Owen, Huxley and others.

The impregnated ova of the *Aphis* are deposited at the close of summer in the axils of the leaves of the plant infested; retaining their vitality throughout the winter, these ova are hatched by the returning warmth of the spring: a wingless hexapod larva is the result. In the pseud-ovaria of these imperfect females, there bud forth pseud-ova, which rapidly develop into similar imperfect females. At this season no winged males have appeared. This process of agamic multiplication continues throughout the summer. If the external conditions, such as warmth and nutriment, continue favourable, eight or more successive generations may be thus produced. But, when the weather becomes cold and the supply of sap fails in the plant, perfect males and females are produced, which by gamogenesis reproduce fertilized ova, thus completing the cycle.

Further experiments have shown that, in such cases, the rapidity of the agamogenesis is proportionate to the degree of warmth and nutrition; and that, if the temperature and food-supply be artificially maintained, the agamogenesis continues throughout the winter. When the favourable conditions have been kept up for several successive years, agamogenesis has likewise continued. In short, it seems probable that this agamic reproduction may be continued indefinitely, if all the requisite conditions be fulfilled.

Thus, in these creatures, the summer brood, living under favourable conditions of nutrition, reproduce agamically imperfect females; whereas, in the autumn, under less favourable conditions of nutrition, perfect males and females are produced. That this is due to the external conditions, and not to fixed cyclical routine in the life-history of the organism, may be inferred from the fact, that in the favourable environment of a greenhouse, the agamic production of imperfect females may continue for years.

This connexion between sexual reproduction and such diminished nutrition as makes growth relatively slow, was first fully made known by the celebrated biologist Caspar Friedrich Wolff, chiefly from the study of the process in plants. Viewed in this light, gamogenesis is seen to be nothing but a particular case of cell multiplication; and impregnation merely one of the many conditions which affect the process.

Seeing that the action of the sperm-cell on the germ-cell was the cause of its development—for before it was deficient in this respect—and bearing in mind such considerations as the above, Wolff was led to regard the former as nutriment in its highest perfection, supplied to the germ-cell from without, instead of through the ordinary channels.

If we ask modern biologists how fertilization causes the ovum to grow and proliferate, they reply that it is due to the action of local bio-chemical or zymotic changes, incited by some substance appertaining to the spermatozoön, which probably concentres in its centrosome or nucleus, and is therefore exceedingly minute as to its quantity. According to Boveri, the ripe ovum comprises all the structures and qualities necessary for growth, except the centrosome, which is supplied by the spermatozoön originating the process; Loeb, however, considers that the spermatozoön acts as a catalyzer, merely accelerating a process which starts of its own accord.

The result of some very remarkable experiments in the artificial production of ovular exegesis, especially point to the importance of chemical stimuli.

Under normal conditions, the growth of the egg of the annelid *Chætopterus*, pauses at the first polar mitosis until fertilized by the spermatozoön, when mitosis is resumed, and both polar bodies are formed.

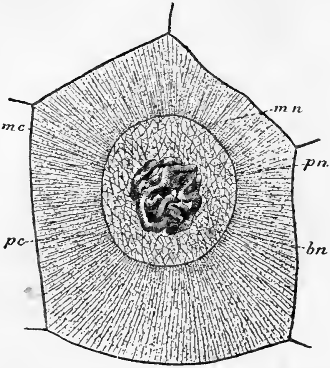


FIG. 10.—A TYPICAL EPITHELIAL CELL (CARNOY).

MC, Cell wall; *pc*, cell protoplasm, showing radiating reticulum, enclosing fluid plasma; *mn*, wall of nucleus; *pn*, nuclear substance, showing reticulum andj plasma; *bn*, contorted bend of nuclein or chromatin.

Mead has shown that the same effect may be produced, without fertilization, by placing the eggs for a few minutes in a weak solution of chloride of potassium.

Hertwig demonstrated that the unfertilized eggs of sea-urchins may be incited to mitotic multiplication, by treating them with weak solutions of sulphate of strychnine.

Morgan found that the unfertilized eggs of sea-urchins and other echinoderms, placed for an hour or two in sea-water, to which 2 per cent. of the chlorides of sodium, potassium, or magnesium had been added, would—when replaced in normal sea-water—enter on active segmentation, the entire mitotic system being evolved under the incitation of the chemical stimulus. Morgan also repeated and confirmed Hertwig's experiments, as to the similar effects caused by sulphate of strychnine.

The climax of these experiments was reached when Loeb, by carefully regulating the strength of his solutions of the above-mentioned chlorides and other reagents, achieved the full development of the embryo from the unfertilized sea-urchin's egg. Loeb also found that short immersion of the unfertilized sea-urchin's egg in sea-water, to which a small quantity of acid or alkali had been added, would start segmentation. It was subsequently shown by Matthews and others, that similar changes could be incited by deprivation of oxygen, by heat, mechanical agitation, ether, alcohol, chloroform etc.; in short, it seems as if any means capable of

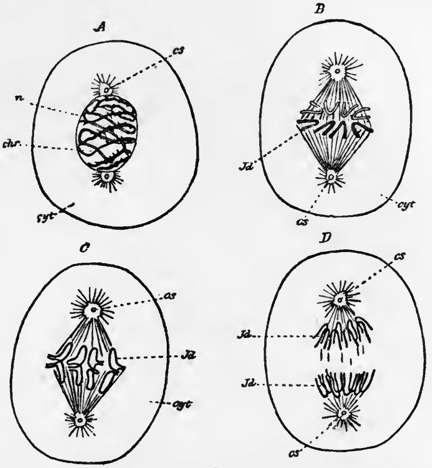


FIG. 11.—DIAGRAM OF NUCLEAR DIVISION (WEISMANN).

A, Cell with nucleus (*n*), and centrosomes (*cs*), preparatory to division. The chromatin forms a thickened spiral thread (*chr*). B, The nuclear membrane has disappeared. Delicate threads radiate from the centrosomes and form a nuclear spindle, at the equator of which eight chromosomes or nuclear loops (*Jd*) are arranged, formed by the splitting up of the spiral thread of chromatin in A. C, The chromosomes have each become longitudinally split into two, and are about to be drawn apart by the spindle threads, the daughter loops passing towards the poles of the spindle, as in D. The cell body then divides, each of the resultant cells containing a centrosome and eight nuclear loops.

producing localized liquefaction of the egg protoplasm, may suffice to originate mitotic proliferation.

Since the nucleus is so largely concerned in the formative changes which cells undergo, it is here necessary to refer briefly to its leading structural features. Under ordinary circumstances, the nucleus usually presents as a more or less globular vesicle embedded in the cytoplasm. It comprises a very fine protoplasmic reticulum, the meshes of which are filled with granular fluid (plasma). In addition to these achromatic substances, the nucleus also comprises a distinctive proteid phosphorus-containing substance called nuclein, or from its staining readily chromatin. In young cells, this substance often presents as a long irregularly contorted filament (Fig.10); but, in mature cells, it is usually condensed into one or more spherical or irregularly shaped masses, which constitute the nucleoli. It is in this chromatin constituent of the nucleus, that the formative properties of the cell seem specially to concentre; and, as it is the only nuclear substance which passes directly from cell to cell during proliferation, it is believed to be the material bearer of hereditary tendencies. In cells about to undergo division, besides other changes, the nuclear chromatin experiences a remarkable series of transformations, assuming successively the forms of a coil, wreath, star etc., the outcome of which is that the chromatic formation is eventually resolved into a definite number of rod-shaped chromatin bodies, known as chromosomes, which split lengthwise as the cell divides—half of each going to the nucleus of the daughter cells. The chromosomes themselves are aggregates of minute chromatin granules (chromomeres).

Every species of animal has a fixed number of chromosomes, which characterizes the division of all its cells; for mankind the number has not yet been certainly determined, but it is generally believed to be sixteen, although some cytologists put it as high as thirty-two, one-half of the number being derived from each parent. The essence of this process of division is, that the chromatic thread, whether continuous or discontinuous, splits throughout its entire length into two exactly similar halves; which are then transported in opposite directions, to the respective poles of the achromatic spindle, whence they enter into the formation of the two corresponding daughter nuclei, each of which thus receives its half share of the chromatin, the movement being effected and the spindle formed under the influence of the centrosomes.

All somatic cells multiplying by mitosis are thought to divide in this manner, the nuclei of the daughter cells having exactly as many chromosomes, as the parent cell.

In 1883, Van Beneden discovered that the nuclei of conjugating germ-cells, contained only one-half of the number of chromosomes characteristic of the somatic cells; and subsequently it was proved that this "reduction of the chromosomes" was a universal feature in the maturation of gamogenetic germ-cells. The peculiar feature of the process is, that the chromatin is rearranged and redistributed, without the loss of any of its essential constituents. It is clear that this reduction is a preparation of the germ-cells for their subsequent union; and the means by which the number of chromosomes is kept constant for the species. In fact, the essence of fertilization consists in the placing in juxtaposition of an equal number of the chromosomes of each parent; so that the offspring may contain all the essential constituents of the chromosomes of both parents in about equal measure. Weismann believes that this reduction is effected by the extrusion of the second polar body, which removes with it the one-half of the chromosomes not needed for gamogenesis.

Recent researches seem, however, to indicate that similar reduction may also occur in the chromosomes of somatic cells, under certain conditions at present but little understood; hence, it is evident that the problem of reduction and its significance, is still far from having been adequately solved.

### Tumour Growth.

All that we know of tumours indicates, that they grow and are nourished like normal parts of the body ; hence, the growth of tumours, like normal growth, is influenced and determined—directly or indirectly—chiefly by the conditions of nutrition, as above set forth.

We have already seen that the germs of histioid tumours are cells of somatic origin ; and that the essence of the neoplastic process consists in the awakening, in these cells, of more intense power of growth and proliferation than is normal.

Viewed in this light, tumour formation may be regarded as a disturbance of the rhythm of growth, by the interpolation in the developmental series of redundant agamic cell generations, owing to altered conditions of nutrition.

Thus the growth of cancers—like discontinuous growth in general, of which it is but a particular case—is the outcome of a disintegrative process, being distinctly related to the decline of growth—" senescence " —of the body in general, and especially of the particular local tissues. Hence, while the forces of growth, development, and reproduction are in greatest activity—during the periods of pre-natal life, infancy, childhood, adolescence, and even adult age—the tendency to this disease is comparatively small. In both sexes, it begins to be of great frequency in the post-meridian period.

Thus the tendency to cancer-growth waxes, as the developmental and reproductive activities wane. The antagonism between the forces of genesis, growth, development, and expenditure, is the same in pathology as in physiology. In this we see illustrated the universal biological law : that growth varies according to the surplus of nutrition over expenditure. So long as the surplus exists, that is to say, while growth is active and nutrition relatively high, simple continuous increase is maintained ; but, when growth declines and nutrition is relatively low, that is to say. when it is nearly equalled by expenditure, new centres of development are apt to arise, and growth tends to become discontinuous. Changes of nutrition determine the transition from the one to the other mode of increase ; and so favour the growth of cancer and other tumours, as I have previously indicated.

The physiological paradigms of the neoplastic process are to be found in gemmation or agamogenesis—especially in that form of it called metagenesis, in which the new formations bud out, not from special organs, but from somatic elements of the parent, whether these are situated externally or internally—and even in parthenogenesis. *In excelsis* all of these forms of growth tend to be discontinuous, and they are essentially of reproductive import ; but it does not necessarily follow that such is always their destiny—the process may have a more or less abortive ending, eventuating for instance in tumour formation.

When agamic processes of this kind end in the formation of new individuals, it may be assumed that this is a result of their germinal cells having acquired complete emancipation from the integrative control of the parental organism ; and, conversely, when only such abortive products as tumours are evolved, the emancipation of the germinal cells from this control may be assumed to be much less complete.

The fundamental nature of the ætiological connexion between these processes and the conditions of nutrition, I have already sufficiently indicated.

In mankind and the higher animals, except in the very earliest stages of ontogenetical development—as we have already seen—no cells (except the ova, which are so differentiated that they cannot respond, until they have undergone maturation and fertilization) are ever completely emancipated ; hence in these, instead of new individuals, such abortive formations as tumours result.

From this standpoint, tumour formation may be regarded as a lapse from predominant gamogenesis, in the direction of agamogenesis ; for, as the individuality of tumours especially indicates, the process is essentially of a reproductive or disintegrative nature.

In like manner, the different qualities manifested by malignant and non-malignant tumours may be interpreted, as I have explained in Chapter VII.

I have previously had occasion to refer to the misleading efforts of some biologists, to indoctrinate belief in a fundamental specific distinction between somatic and germ cells, which the most detailed histological analysis of cellular structure fails to support ; and which is contravened in the plainest manner, by many of the most fundamental and important facts in the whole range of biology, as I have elsewhere indicated.

With regard to this doctrine, it may truly be said, that it has no real foundation in fact : it is, indeed, the outcome of " muddy speculation," starting from an essentially faulty conception ; and, as such, it must be regarded as being entirely outside the pale of scientific truth.

As E. B. Wilson, the chief exponent of modern cytological knowledge for English-speaking people, has so well said, in the latest edition of his useful book :[1] " All the facts at our command indicate, that the tissue cell possesses the same morphological organization as the egg-cell, or the protozoan ; and the same fundamental physiological properties as well."

There can, then, be no doubt, as Spencer and Darwin surmised, that the fundamental properties of somatic and germ cells are the same in kind, and that they differ only in degree.

In the growth of malignant tumours, as in the growth of normal tissues, differentiation and proliferation seem to be inversely related. In a certain general way, it may be said of the metabolism of malignant tumours, that the habit of growth predominates over the habit of function (Adami). In some animals, it has been found that differentiation is concomitant with the loss of certain nuclear structures ; and Boveri has suggested, that the exceptional regenerative power of some organisms, may be due to retention in latent state, by differentiated somatic cells, of reproductive properties derived from the fertilized egg. It may be inferred from these considerations, that growing tumour germs owe their unusual proliferative capacity, to the relative non-involvement of their nuclear substance in the specific changes which determine differentiation.

[1] " The Cell in Development," etc., 1904, p. 291.

### Recapitulation and General Conclusions.

In concluding this stage of the argument, a brief recapitulation of the chief items thereof may be useful.

Besides such general causative factors of growth as I have had occasion to mention, which are chiefly the outcome of intrinsic forces, there are also other considerations which affect the process. Thus, for instance, with the growth from the ovum, although the stimulus of fertilization is generally necessary for its accomplishment; yet, the process starts independently, and is merely accelerated and completed thereby. That this stimulus is not always necessary, is shown by the life-history of the common bee, whose unfertilized ova grow "spontaneously" into males, while the very same ova, when fertilized, grow into females; of like import are the cases of "true" parthenogenesis, wherein cells—which are indistinguishable from ova—grow into new beings, without any such external stimulus. In metagenesis, and in other forms of agamogenesis, we see unspecialized somatic cells of diverse parts of the body—which are certainly neither germ-cells nor ova in the usually accepted sense of these terms—nevertheless, endowed with the power of growing into new individuals, without any other stimuli than those provided by the rhythm of growth and favourable conditions of nutrition. Then, finally, we see growth from the ovum incited, and even urged to its completion, by various chemical stimuli and other extrinsic factors. Thus, the evidence that the reproductive properties of somatic and germ cells are the same in kind, and differ only in degree, is full and complete.

It is in the light of such considerations, that the problem of the growth of histioid tumour germs must be studied. Indeed, it seems certain that the conditions, both general and special, which determine tumour growth, are similar to those concerned in the regulation of these its physiological paradigms.

Thus, in the pathological as in the physiological process, besides the general causative factors of growth, various other conditions seem to affect the process.

With regard to the influence of nutrition, of which I shall have more to say in the sequel, I will now only remark; that tumours grow, because the bodies of the affected persons contain an abundance of materials suitable for their nutrition, and stimulating to their formative metabolism.

Thus, cancerous tumours consist almost exclusively of albuminous or proteid substances; and, it seems not unreasonable to suppose, that their growth may be favoured by excess of these substances in the body—and especially of such of them as serve as nuclear pabulum. When excessive quantities of such highly stimulating forms of nutriment are ingested, by persons whose metabolism is defective—whether by reason of senescence or otherwise—there may thus be excited, in those parts of the body where proliferative processes are still potentially active, such excessive and disorderly cellular proliferation as may eventuate in cancer. However this may be, I am persuaded that the ascertained facts justify the belief, that there is a certain relation between the conditions of nutrition and the incidence of cancer growth.

It seems to me quite clear, that the growth of malignant tumours is also favoured by the altered metabolism of the body, consequent on decline of the reproductive function. The age-incidence of the disease accords with this; and of similar import is the fact, that malignant growths in women occur with great and altogether disproportionate frequency, after removal of the ovaries for various non-malignant affections; after the destruction of their essential elements in the course of disease; and in cases of congenital absence or defect thereof, of which I shall have to say more in the sequel. The great frequency of malignant growths in castrated cattle of both sexes, to which Sticker[1] has specially called attention points to the same conclusion; thus, of 200 bovine animals with malignant tumours tabulated by him, no less than 100 were castrates; and of 120 horses with malignant tumours, 51 were castrates.

It has been suggested that other organs, besides the sexual glands, may also influence the general metabolism in such a way, as to retard or favour the growth of cancer. Although, in this connexion, there is absence of any decisive evidence, such as is forthcoming in favour of the rôle of the sexual glands; it seems desirable, in accordance with the plan of this work, briefly to review this line of inquiry, especially as it may throw some light on the obscure processes of metabolism, with which tumour growth is so intimately bound up.

The growth of the epithelial tissues of the body certainly varies much, and is differently conditioned, at different periods of life. In infancy and childhood, as compared with the other tissues, the epithelia are comparatively inactive; and, it seems probable, that the immunity of children from malignant epithelial growths, is in some way connected with this physiological quiescence.[2] By what means then, in the healthy body, is epithelial growth inhibited and kept within due limits? To this query, the chemical physiologist answers: that it is due to certain bio-chemical reactions, in which enzymes play a leading part—"anti-epithelial" substances being thus formed, which circulating throughout the body check the growth of epithelial cells. In like manner, the chemical pathologist refers the exuberant epithelial growth of cancer, to absence or deficiency of these special substances.

The organs more particularly concerned in influencing these hypothetical processes are, according to Sajous, the adrenals, the thymus, the thyroid, and the anterior part of the pituitary body—the adrenal influence predominating. Thus Sajous[3] says: "Certain growths, particularly the more malignant forms of sarcoma and carcinoma, seem closely connected with adrenal insufficiency and its normal consequences. We have seen that trypsin, fibrinogen and the oxidizing substance, were simultaneously necessary to ensure the destruction of cells *in vitro*; and, furthermore, that this process required, in addition, the presence of alkaline salts. That the destruction of worn-out or degenerated cells, is a function of these very elements in the blood, is evident. Insufficiency

[1] *Arch. f. klin. Chir.*, 1902, Bd. lxv., Heft 3 and 4. [2] *Vide* Chapter XV.
[3] "Internal Secretions," 1903, vol. i., p. 785, Philadelphia, U.S.

of the adrenals therefore, by reducing the relative proportions of these four constituents in the blood-stream, must correspondingly inhibit this physiological process in all parts of the system."

In comparatively recent times some remarkable instances have been reported, which show that there is some ætiological connexion between ovarian and adrenal integrity; and the growth of malignant tumours. Thus, as I have specially pointed out, in a publication on "Precocious Sexual Development,"[1] this anomaly is fairly often associated with malignant ovarian and adrenal tumours. Bullock, Sequeira, Linser, Adams[2] and Guthrie[3] have lately reported additional examples of this kind, associated with malignant adrenal tumours; and I have[4] elsewhere cited instances of malignant tumours of various parts of the body, concomitant with non-malignant adrenal tumours.

Here also it may be mentioned that Drs. Beard and Shaw-Mackenzie,[5] have ascribed cancer growth to perverted metabolism caused by hypothetical failure of pancreatic secretion,[6] especially of trypsin; and they claim to have cured "Jensen's tumour" in mice—which so often undergoes spontaneous cure—with injections of this substance.

Whatever element of truth may be concealed in these obscure processes, it appears to me that these therapeutic suggestions go far beyond what is warranted by the known facts; indeed, it is only with regard to thyroid medication—which seems to exert beneficial influence on some hyperplastic cutaneous maladies, and even on certain cancerous growths—that we can be said to have any facts at all worthy the name, and these are far from warranting such sensational inferences as have been drawn.

If then I have referred to these matters at all, it is because of the possible prospective value of this kind of research, rather than for anything that has as yet been ascertained.

We have already seen that the tissue cells may be incited to abnormal growth and proliferation by some traumata, by the toxins of certain microbes, by various chemical, electrical, thermal, mechanical, and other extrinsic agencies; although none of these seem able, *per se*, to carry the process on to true tumour formation. Thus tumour germs resemble ova, in that they generally require to be matured and stimulated in a particular way, before their potential proliferative power can become actual.

From this standpoint, the problem of cancer growth resolves itself into a research, to determine the particular way in which the cells of tumour germs may be incited to unfold—in sufficient measure—their potential proliferative capacity.

Although it is probable that in the past, the value of extrinsic factors, as formative stimuli, have been underrated; it, nevertheless, seems probable, from the whole course of ontological growth, that, in tumour formation, as in normal growth, intrinsic factors usually predominate.

[1] *British Gynæcological Journal*, May, 1902.
[2] Transactions of the Pathological Society, London, 1905, vol. lvi., p. 189.
[3] *British Medical Journal*, September 21, 1907.
[4] Chapter XIII.
[5] *Medical Press and Circular*, December 20, 1905, p. 661; see also Dr. Shaw-Mackenzie's "Nature and Treatment of Cancer," 1905.
[5] As will be mentioned later on, cancer of the pancreas is comparatively rarely associated with glycosuria.

If we ask cytologists to explain, How it is that ova sometimes develop parthenogenetically? they reply, that it is due to imperfect maturation; for, cells undergoing this kind of growth, extrude only a single polar body, and consequently undergo no reduction of the nuclear chromosomes, which is effected by the extrusion of the second polar body, and is preparation for fertilization. Pursuing the analysis further, they maintain that, in parthenogenesis, the second polar body is not really absent, but only abortive; and that this kind of growth is the result of the self-fertilization of the ovum, by its abortive second polar body.

There are, however, good reasons for believing, that this interpretation of the process is far from being adequate, since the ova of certain arthropods have been seen to develop parthenogenetically, although —like ova which require fertilization—they have produced two polar bodies, and have undergone reduction of the chromosomes. Nevertheless, pathological cytologists are now asking, whether conditions of this kind may not play a part in the growth of tumour germs? So far as I know, no one has ever observed in the germ-cells of cancer, maturation phenomena like those seen in normal or parthenogenetical ova; that is to say, the formation of polar cells—unless, indeed, some observations by Paterson [1] may be interpreted in this sense. It has, however, long been known, as specially indicated by Hansemann,[2] that among the numerous mitotic irregularities of growing cancer cells, a deficiency of the chromosomes ("hypochromatic") is often noticeable; lately, Farmer, Moore and Walker,[3] have described the occurrence of reduction of the chromosomes ("heterotypical mitosis")—like that normally met with in maturing germ-cells—as being a constant and special feature of the growth of malignant tumours.

Considering how little is known as to the occurrence of this reducing process in human tissues, cytologists not even being in agreement as to the precise number of chromosomes proper to ordinary somatic mitosis, this generalization seems rather premature; and, it accords with this, that reduction of the chromosomes in somatic mitosis has already been reported in various processes, having nothing to do with cancer; and it has even been found possible to produce it artificially by chemical stimulation etc., as previously mentioned.

It is generally stated that among tumours, only the malignant ones exhibit this form of nuclear arrangement; but Bonney [4] has met with it in condylomata, and in ovarian papillomata.

Since then reduction of the chromosomes is not constant in malignant tumours, and since it occurs in the absence of malignancy, whatever its significance may be, it cannot be regarded as specific of cancer. It is even just possible, that reduction may eventually turn out to be merely a phase of senescence in certain tissues.

It was long ago remarked by pathological cytologists,[5] that the

[1] *Practitioner*, May, 1904.
[2] *Arch. f. path. Anat.*, 1890, Bd. cxix., S. 299; also 1891, Bd. cxxiii., Heft 2.
[3] "Cytological Investigation of Cancer," Liverpool, 1906.
[4] Transactions of the Pathological Society, London, 1905.
[5] Transactions of the Pathological Society, London, 1888, vol. xlix., p. 409 (Shattock and Ballance).

nuclei of growing cancer cells have a tendency to shed their chromatin into the cytoplasm, as a sort of preliminary to division; and to this source the detached nuclear fragments, described by Foà[1] as *corps colorables*, were generally ascribed. Paterson[2] has lately reinvestigated this subject, and found that during mitosis certain of the nuclei throw out processes like pseudo-podia, this being the first stage of budding, or the beginning of the migration of the nuclear chromatin from the cell. The appearances seemed to indicate, that such extruded chromosomes, and the remainders of such reduced nuclei, may unite by mitosis with similarly affected nuclei from other adjacent cells, introducing conditions having some resemblance to those described in the formation of abortive polar bodies, and in the maturation of parthenogenetic eggs. Whether this interpretation of the mechanics of cancer growth will eventually be substantiated, remains to be seen.

Pathologists have, of course, long been familiar with the conception which ascribes the initiation of malignant growth, to the conjugation of the cell of a cancer germ, with some adjacent somatic cell, as described by Strœbe,[3] Hansemann, Klebs and others; but it cannot be said that the doctrine thus advanced carried much conviction. Lately, as the outcome of such research tendency as we are now pursuing, this matter has again cropped up.

That leucocytes may not unfrequently be found between, and even within, the constituent cells of cancerous tumours, has long been well known. Lately, Farmer, Moore and Walker,[4] examining quite young cancer formations, found that the histological appearances indicated a kind of conjugation between the local epithelial cells and included leucocytes, with mixing of the chromosomes of the respective nuclei during mitosis, but apparently without reduction; and to this they ascribe cancer growth.

In studying the cytology of cancer pathologists, as a rule, have paid but little attention to the centrosome, to which biologists attach such great importance, as the directing centre of formative changes.

In 1893, however, Galeotti and Lustig[5] clearly identified the centrosomes in cancer cells; and published descriptions and drawings of them. In resting cells, they found a single centrosome in a depression at the margin of the nucleus; but, in cells entering on mitosis, the two centrosomes were found one at each apex of the mitotic spindle.

Borrel[6] next identified certain rounded "endocytes" or "inclusions" commonly found in cancer cells, and often described as sporozoa or coccidia, as being the cell archoplasm with its contained centrosomes, with which he had previously gained familiarity when studying the spermatogenesis of guinea-pigs.

Le Count,[7] as the outcome of a similar study, supported these con-

[1] *Gaz. degli Ospitali*, February 2, 1893.
[2] *Op. cit.*
[3] Ziegler's *Beitrage z. path. Anat.*, 1891, Bd. xi., S. 1.
[4] *British Medical Journal*, 1905, vol. ii., p. 314; and *op. cit.*
[5] Ziegler's *Beitrage z. path. Anat.*, 1893, Bd. xiv., S. 225.
[6] *Ann. de l'Inst. Pasteur*, 1901, vol. xv., No. 2.
[7] *Journal of Medical Research*, vol. vii., p. 383.

clusions; while Hansemann also included the archoplasm, as one among the many conditions which give rise to "endocytes" in cancer cells.

Benda,[1] having found intact centrosomes in cancer cells, in which "endocytes" were also present, claims that this disproves Borrel's interpretation as to their analogy.

Farmer, Moore and Walker,[2] having lately retraversed the same ground, conclude that these "endocytes" represent not the centrosomes, which were discernible elsewhere in the cells; but the cast-off archoplasmic vesicle, in which the centrosomes were originally contained.

Whatever the real nature of these "inclusions" may be, they are evidently not peculiar to cancer, as Greenough[3] and so many others have shown.

Indeed, it is as yet far too early to estimate the precise significance attaching to the various recent cytological findings in cancer cells; but, already it can be clearly discerned, that none of them are specific of malignancy.

The most searching morphological investigations, having failed to reveal any specific mark of malignancy, pathologists are now seeking for some chemical *materies morbi*.

Like so many of our modern conceptions, this is an old favourite in new dress. Over half a century ago, in the days of J. Müller[4] and Lebert,[5] the chemistry of tumours was very thoroughly studied, with the same objective in view; but no specific substance was discovered. The general outcome of these researches was, that the greater the malignancy of the tumour, the more albuminous substances predominated in its composition; hence Rokitansky[6] proclaimed that diseased ("kakoplastic") albumin, was the cause of all true malignant tumours.

Modern physiologists have advanced the hypothesis, that the development of particular structures is determined by specific formative substances, which incite corresponding kinds of metabolic activity and differentiation: the nucleus, they regard as a storehouse of ferments, which pass out into the cytoplasm, and there set up specific activities.

In like manner, some modern pathologists ascribe the initiation of cancer growth, to bio-chemical disturbance of the relations normally subsisting between cell, nucleus and protoplasm; in which, as the result of catalysis, there is assumed to be some unusual mingling of enzymes.

According to Blumenthal[7] and Hemmeter,[8] cancer cells differ chemically from somatic cells, comprising substances that have hitherto not been found in the normal body; while Petry claims that there is a special intra-cellular cancer ferment—which has been called "malignin"—by means of which cancer cells are endowed with their special qualities. These conceptions have very little basis in ascertained fact; they are

[1] *Verhandlungen d. deuts. Gesellsch. f. Chir.*, 1902, No. 31, S. 73.
[2] Proceedings of the Royal Society, 1905.
[3] Third Report of the Croft Cancer Commission, Boston, U.S., 1905.
[4] "Ueber den feineren Bau und die Formen der krankhaften Geschwülste," 1838.
[5] "Traité d'Anat. Path.," etc., Paris, 1857.
[6] "Handb. der allgem. path. Anatomie," Wien, 1846, S. 530.
[7] *Berlin. klin. Woch.*, 1905, Nos. 12 to 15.
[8] *American Journal of Medical Science*, April, 1903.

rather the outcome of *a priori* considerations, and differ but little from Rokitansky's "kakoplastic" albumin, and other kindred speculations, which have long since been forgotten.

Thus chemistry, like morphology, has failed to reveal any specific cancer substance, from whose presence this malady must result.

In the light of these long-continued and repeated failures, we shall probably not be far wrong in concluding that there are no specific cancer substances, other than such as are concerned in determining the specificity of the various physiological tissue elements.

It will be gathered from the foregoing, that far more may be learnt, as to the real nature of the cancerous process and the conditions which determine it, from study of the general laws of growth and its rhythm, and of their relation to the conditions of existence, which comprise nutrition; than from the mere pursuit of details — morphological and chemical—in ultimate analysis, which lead to nothing more stable than a chaos of hypothetical "enzymes," or to other equally unreliable metaphysical notions—such as credulous and unscientific epochs, like the present, are particularly apt to engender.

## Growth, Repair, Regeneration, and Tumour Growth.

It now remains for me to offer some further remarks on that part of this important subject, which relates to repair and the regeneration of lost parts, as prototypes of tumour formation.

In the case of crystal formation, it is obvious that the whole aggregate exerts a force, which constrains newly integrated units to take a certain form; and thus crystals are enabled to repair injuries.

It seems probable that the rearrangements of organic units, which characterize the processes of repair and regeneration in animals, are determined in a similar way.

According to Herbert Spencer, cells capable of growth completely uncontrolled and placed in fit conditions, naturally tend to arrange themselves into the form of the organism whence they originated; thus, a small detached bit of a Hydra, soon moulds itself into the shape of an entire Hydra.

On the other hand: "Cells which form a small group involved in a larger group, are subject to all the forces of the larger group, will become subordinate in their structural arrangements to the larger group, will be co-ordinated into a part of the major whole, instead of co-ordinating themselves into a minor whole"; hence, the cellular mass which buds out in place of a lobster's lost claw gradually assumes the form of a claw, that is to say, it has its parts so moulded as to complete the structure of the organism.

It is thus evident that the organism, as a whole, exercises such controlling power over the newly forming part, as to make it a reproduction of its predecessor.

Structurally regarded, the new formation of repair closely resembles that of similarly situated tumours; and between the reparative and neoplastic processes there is obviously an affinity—such differences as exist being in degree rather than in kind. Indeed, the grand difference lies in this : that whereas the new growth of repair is definitely limited and merely suffices to replace what has been lost, the pathological new growth knows no such bounds. In the latter case, the normal subordination of the local process to the specific hereditary tendency of the whole, has been diminished or has ceased to exist. Such a local abnormality of growth may then acquire a fixed character, becoming incapable of further change—except within the limits imposed by its acquired character—and thus a tumour is formed.

It has now been clearly established by the criterion of mitosis, that the new formation of repair is produced by the active growth and proliferation of the tissue elements of the affected part, in which leucocytes and other cellular elements *ab extra* are not essentially concerned.

It has also been ascertained that the rapidity of proliferation in pathological regeneration, is greatly in excess of that by which the normal wear and tear is made good.

By the same method it has likewise been determined, that reparative processes are most prone to arise and are most efficient, in those tissues where cells capable of growth and proliferation most abound.

It has also been proved that the reparative process, like tumour formation and the growth *ab ovo*—of which latter it is but a modified superinduced repetition *in partibus*—is independent of nervous (trophic) and vascular influences (inflammation etc.).

As in the course of normal development, cell derivatives of the different blastodermic layers are never transformed into each other ; so, in the reparative new formation, no such metamorphosis ever occurs. Hence, no structures of new and specific type are to be found in the new formation of repair ; whose elementary constituents, as a rule, resemble those of the physiological tissues both genetically and histologically.

Such at least appears to be the state of affairs in the highest organisms ; but, in the lower kinds, as in the Hydra, no such distinction is apparent.

It seems probable that the tissues of all organisms are constantly being destroyed, in the normal exercise of their functions ; and that a certain capacity for such physiological repair as is necessary for making good these losses, is inherent in all organisms.

Thus, at certain periods of the year, many animals by a spontaneous and natural process lose certain parts of their body, which are subsequently renewed, *e.g.*, the fall of the stag's horn, the moulting of birds, the shedding of the cuticle of serpents and the shell of crustacea ; while holothurians, regenerate the digestive tube, after its voluntary expulsion etc.

Similarly, under pathological conditions, wounds heal, fractured bones are repaired, and lost parts may be regenerated.

This property is possessed by mankind and the higher animals in but a very limited degree ; but its perfection in some of the lower animals is truly astonishing.

Moreover, reparative processes are proportionally much greater in the young than in the old of all species, being greatest of all in the early embryo ; and their efficacy gradually diminishes with advancing life.

Hence the larvæ of amphibians, which present many parts that in other animals are developed only in the embryo state, have also greater powers of regeneration than the perfect animals ; and in the larvæ of insects lost parts are often reproduced, which in the perfect insects cannot thus be replaced.

The various parts and organs of animals are also diversely endowed in respect to this faculty, *e.g.*, lizards regenerate the tail, but not the limbs etc.

The general law to which these processes conform, is identical with that which holds for reproduction in general ; that is to say, it is greatest where organization is lowest, and it almost disappears where organization is highest.

It also appears as if the capacity for repair were inversely related, to the amount of energy consumed in the growth and development of the individual, and in maintenance of the same.

Thus, when an animal so low in the organic scale as the *Stentor*, is divided transversely into two or three parts, each of these grows into a complete *Stentor ;* and this, even when the slices removed are only half a millimetre thick. It appears, therefore, as if each of the units of which a *Stentor* is composed, is capable of regenerating the whole organism.

Even among animals much higher in the organic scale, such as the polypes, similar phenomena are met with. Thus, the experiments of Trembley with Hydra show, that when this creature is divided longitudinally or transversely, or when small portions are merely cut out of its body, in all such cases the separated fragments grow into perfect polypes. Even when the creature was cut up into as many small pieces as possible, each of these became a perfect Hydra ; by methods of this kind, from a single polyp Trembley produced fifty, each of which grew into a perfect individual.

In this connexion the question naturally arises, as to how small a portion of a metazoon organism may contain the force necessary for the reproduction of the entire individual ? In the case of Hydra, it appears as if almost any minute group of cells, severed from the perfect organism, sufficed for this purpose.

In other lowly organized beings, the power of reproducing new individuals is not merely manifested by separated portions of almost any part of the organism ; but, in some cases, subdivision even to the ultimate morphological units, does not destroy this power—isolated structural units are, in fact, adequate for this purpose.

In like manner, as recent experimental researches have shown, each of the cells (blastomeres) into which in the higher organisms the fertilized germ divides, also retains all the properties requisite for producing the entire organism ; and this is so even up to the eight- or sixteen-cell stage (Wilson, Driesch, Zoja etc.). Moreover, pieces excised from globular blastulæ before invagination, have grown into perfect larvæ ; and Roux found that half embryos, evolving from detached blastomeres of the frog's egg, finally regenerated more or less completely the missing half.

It appears to me that facts of this kind, which can easily be multiplied, contradict Weismann's theory, as to there being specific distinction between somatic and germ cells.

Among other experiments on Hydra, Trembley divided polypes longitudinally, when, in less than an hour, each half had rolled itself and united the cut edges, so as to constitute each a fresh polyp ; he likewise divided them transversely, and having brought the divided halves together, found that before the close of the day they had firmly united.

In like manner, he even succeeded in causing the anterior and posterior halves of two different polypes to unite ; and the resultant polyp then budded and produced young polypes, both above and below the line of union.

Longitudinal narrow bands cut out of the body of Hydra, too slender for their borders to unite to form a tube, nevertheless regenerated complete polypes, the digestive canal being formed by the development of a new cavity in the substance of the separated fragment.

Here I must mention a remarkable fact : several experimenters have found that completely everted polypes still continue to flourish—ectodermal cells quickly taking on endodermal functions, notwithstanding their obvious morphological differentiations.

Imperfect division produced polypes with two or more heads: Trembley slit one into seven pieces, leaving them connected by the root, and the Hydra became seven-headed ; he cut off the seven heads, and they soon sprang up again. By laying open a polyp longitudinally, and then notching it in different directions, he produced a compound, arborescent, plant-like animal with many heads and tails.

It was specially noticed that these experimentally-produced polypes grew much larger, and were far more prolific, than those that had never been cut ; but, the supervention, of gemmation, markedly retarded the regeneration after injury. Warmth favoured, and cold retarded it.

In such cases as the foregoing, the processes of regeneration and reproduction by gemmation are seen to be identical.

*Tubularians* and many other hydroids, can regenerate the " head " (*i.e.*, hypostome, mouth and tentacles), after decapitation.

*Planarians* also possess regenerative capacity in a high degree. Dugès saw from eight to ten new individuals formed, from sections of a single animal ; and it has been observed, that these creatures sometimes reproduce themselves spontaneously, in a similar way. When the head is damaged they regenerate a new one.

In the higher *actinozoa,* half an individual will grow into a complete new being ; and star-fishes, such as Nais, may be cut into thirty or forty pieces, each of which will regenerate a new individual.

In the common *earth-worm,* if the anterior segments as far back as the fifth are cut off, the rest of the body will regenerate the lost parts, which comprise cephalic nerve centre, mouth, stomach etc. ; and this kind of regeneration has been known to occur, as many as five times in succession.

Two pieces of different earth-worms that have been transversely severed, when brought into apposition, may grow together, and so form a new worm (Landois).

When, however, worms are longitudinally divided, each half dies.

*Snails* can regenerate parts of the head, including tentacles and eyes, provided that the cerebral ganglion is not injured.

In *insecta, arachnida and crustacea*, entire organs such as extremities, maxillæ, antennæ, eyes etc., may often be reformed after loss, provided that their matrix survives.

In *crustaceans* the power of regenerating lost limbs is highly developed; thus, if the entire leg—except the minute pair of proximal segments—is broken off, a new leg develops from the short stump at the next casting of the shell. In like manner, if the eye of a crab is excised, without injuring the optic ganglion, a normal eye is regenerated.

As we ascend in the scale of organization this power, though diminished, is still considerable.

Among the vertebrata, in the case of *fishes*, regenerative capacity is generally believed to be comparatively deficient; but, it is known that fishes can reproduce lost fins—especially the caudal fin.

Far greater reparative powers are possessed by *amphibians*. In many of these the regeneration of an entire limb or a tail, occurs readily; and this even several times over, although with decreasing completeness. Spallanzani cut off the legs and tail of a salamander six times, and Bonnett eight times, successively; and they were reproduced. In these animals the lower jaw, when damaged, is also reformed, provided the stump is left. As the observations of Götte, Fraisse, and Wendelstadt show, when the fore-limb of a newt (*Triton*) is amputated between the shoulder and elbow, not only is the lost portion of the humerus formed afresh; but the radius, ulna, and all the bones of the wrist and hand, are regenerated accurately, even as regards the number of segments. It seems hardly credible that such a complex of structures could be reproduced, merely by the co-operation of the local proliferating cells, without the agency of some integrative force to direct the process in accordance with the specific hereditary tendency of the whole.

In these regenerative processes, the developmental changes are modelled after those of the normal ontogeny; and, in the one, as in the other case, each specific tissue element only reproduces its own kind of cells. Hence, the regenerative process always proceeds from the injured part—remains of the severed periosteum, endosteum etc., being essential for the process; so that, when the limb is disarticulated at the shoulder girdle and the bones are uninjured, the latter are not reproduced.

In the *Triton*, Blumenbach has seen the eye, with cornea, iris and lens, regenerated within the space of a year; in comparatively recent times, Wolff, Mueller and others, having removed the lens of the eye of larval salamanders, found that it was perfectly regenerated.

The skin of amphibians is readily regenerated after considerable areas of it have been destroyed; and this reproduction comprises not only the whole epidermis, but also the various glands and tegumentary sense organs (Fraisse).

Only the larvæ of the tailless batrachians (frogs etc.), and not the adults, are capable of reproducing lost members; but regeneration is so complete in frog tadpoles, that when the tail is cut off, it is reproduced, together with the notochord.

The tail of a *lizard* is soon restored after it has been cut off; but, as compared with the original tail, the new one is structurally defective in several respects. Thus, instead of the segmented vertebral axis, it often happens that only an unsegmented cartilaginous tube is formed, with no trace of notochord; and, instead of the spinal cord, only an epithelial tube is reproduced, which gives off no nerves: moreover, the scales of the regenerated tail are often markedly different from those of the original one. Lizards are unable to regenerate lost limbs; as also are chelonians, and crocodiles.

In such instances of regeneration as the foregoing, the newly formed part is always very like its prototype; but, I must now mention that the lost part is fairly often replaced by a structure different from the original (*heteromorphosis*). These heteromorphic growths are of special interest, as constituting a connecting-link between the new formations of repair, and tumours.

I have already called attention to the fact that, in pathological regeneration, the rapidity of the growth greatly exceeds the rate of the corresponding physiological process; and it was also mentioned, that polypes produced from dissevered fragments of Hydra grow much larger, and are far more prolific, than those which have never been cut. In accordance with these indications, we find that redundancy is the predominant feature of these heteromorphic manifestations. Thus, the regenerated rays of star-fish are often bifurcated, or present supernumerary parts.

Loeb found that when a tubularian stem is cut off at both ends and inserted in sand, with the oral end buried, a new head is then regenerated from the free end, which was formerly the aboral end. When such a piece was suspended in water by its middle, a new head then formed at each end; while when both ends were buried, neither regenerated. This shows that the regenerative process may be modified by external conditions.

On excising the stomach and ventral nerve-cord of the earth-worm, after having removed the ventral halves of the fourth, fifth and sixth segments, Weldon noted that a new head grew out of the gap, producing an extraordinary double-headed monster.

Dugès found that planarians, notched in the oral region, regenerated with two heads; and, when similarly treated at the opposite end, two tails resulted.

In a crayfish, whose nipping claw had been irregularly amputated, Maggi saw a double claw form in its place; and in other crustaceans similar happenings have been noted.

Among amphibians, many instances of this kind of anomaly have been met with: in the axolotl of his aquarium, Vulpian saw a bitten-off extremity regenerated, and at the same time a redundant digit formed; in certain tritons the same occurrence has been noted; while Piana caused polydactylism in these creatures, by notching the carpus or tarsus with scissors.

In frogs, which as a rule do not regenerate lost limbs, redundant limb-like structures have several times been seen to spring from the stump of an extremity removed by operation.

By cutting off the tail of salamanders, lizards etc., and notching the stump, Loeb and others saw double and even multiple tails form.

It has also been remarked that when the amputated tail of a lizard is reproduced, the scales of the regenerated part are unlike those of the original organ, resembling, indeed, those seen only in certain ancestral forms. This experience recalls the somewhat similar heterotopia met with in certain galls, as previously mentioned.[1]

The experiments of embryologists, at very early developmental periods have yielded results of similar import to the foregoing : thus, by ligaturing the nascent medullary plate of an evolving triton germ, Spemann saw a new head form, from the anterior end of the posterior part of this medullary plate, which was just as perfect as if it had evolved from the anterior part of the undamaged plate, as in the normal course of ontogeny. It is thus evident, that all the complicated structures concerned in the head, can be evolved from parts, which—if development had proceeded normally—would not have participated in the formation of head structures. It may be inferred from these experiments, that each blastomere or group of blastomeres of the evolving germ has the power, when isolated, of forming a new individual.

It seems to me that the neoplastic process is a phenomenon of the same order, as these heteromorphic new formations of regeneration. In both cases the essence of the process is that, at certain points, more intense cell growth and proliferation sets in than elsewhere. The difference between them, is merely one of degree—the emancipation of the proliferating cells from the control of the whole organism, being greater in the latter than in the former case. The precise nature of the resulting structure seems to be determined by the particular relations which each part has with the environment, either habitually in the individual or occasionally in the race.

It accords with this, as I have previously indicated,[2] that, in the higher animals and in mankind, many instances are known in which malignant and other tumours have developed directly from the new formation of repair.

In the highest animals and in mankind, lost parts are never regenerated : in these, it is only single tissues and their derivatives that are reproduced ; but, their wounds heal readily, broken bones are repaired, and in other ways reparative processes are active.

It is, however, alleged that supernumerary digits have been partially reformed after amputation, even in human beings ; and the occasional hetero-morphic formation of imperfect nails on the stumps of normal fingers after amputation, seems to be an outcome of the same tendency in a slight degree.

According to J. Y. Simpson, in early embryonic life, some power of

[1] Chapter VI. [2] Chapters V. and XI.

reproducing lost parts may be met with even in mankind ; and he claims to have demonstrated several instances of the reproduction of rudimentary digits, after the amputation of limbs *in utero* by bands, etc.

Of like import is the recurrence of subungual exostosis of the great toe, when the matrix of the new formation is not thoroughly extirpated ; for, as I have elsewhere shown,[1] this new formation is in its nature akin to digital redundancy at its minimum.

### The Reparative Capacity of the Human Tissues.

In human tissues, the reparative process conforms to the same laws as those which apply to regeneration in general ; thus, this capacity is least in the highly specialized tissues (*e.g.*, muscle and nerve), and greatest in the comparatively undifferentiated (*e.g.*, the epithelial and connective.

Since the discovery of " mitosis " as a criterion of the proliferative activity of the cells, it has become possible to determine accurately both the intensity and the duration of tissue repair, and to trace its histogenesis. By this method it has been proved, that the new formation of repair is the product of the proliferation of pre-existing tissue cells ; and not of leucocytes from the adjacent bloodvessels, as was formerly believed.

Studies of this kind have shown, that in some tissues the constituent cells continue to multiply throughout the life of the individual (*elementi labili*) ; or, at any rate, up to some time after birth (*elementi stabili*) ; and these, as Bizzozero has indicated, repair their losses with great completeness. Such tissues comprise the epithelial—whether disposed as a covering or in glandular arrangement—connective tissue in general, unstriped muscle, bloodvessels, periosteum, bone etc. These are the tissues of which the matrix of histioid tumours are composed.

In another group of tissues, multiplication of the cells by mitosis ceases in early embryonic life, before their elements have assumed specific character (*elementi perenni*) ; these (which comprise the striped muscles and nerve tissues) never regenerate completely, and hardly ever originate malignant tumours.

The process of tissue repair is modelled after the same plan as the process of tissue development in ontogeny, of which it is but a modified superinduced repetition : in both cases, proliferation of the tissue elements, and not inflammation, is the real starting-point, while bloodvessels and nerves are at first absent.

In all these respects, the analogy between the reparative new formation and tumour growth is very striking ; and, as we have already seen, tumours sometimes arise directly from these reparative new formations.

It has lately been shown by Loeb,[2] Fischer,[3] and others, that all the essential histological features of malignancy are reproduced in the behaviour of the epidermis, during the healing of wounds. Thus, the epithelium on each side of superficial cutaneous wounds was found to

[1] *Bristol Medico-Chirurgical Journal*, March, 1904.
[2] *Johns Hopkins Hospital Bulletin*, January, 1898.
[3] *Münch. med. Woch.*, 1906, Bd. liii., S. 2042.

fuse into syncytial masses, whence branching processes budded out, not only bridging the gap, but also growing downwards, into and through the subjacent clot, penetrating the underlying damaged tissues and even cartilage, just as happens in cancer. Indeed, it is suggested that this penetrative quality of the ingrowing cells is due—in the one as in the other case—to enzyme action. However this may be, it is now evident that there is not only anatomical, but also physiological resemblance, in the two processes.

## CHAPTER X

## THE MICROBIC THEORY OF CANCER

Although it appears to me, for reasons set forth in previous chapters, that the influence of extrinsic factors is no more necessary to account for the origin and growth of a tumour, than it is to account for the origin and growth of a tooth or a hair; yet, I think it is a mistake to deny on *a priori* grounds, the possibility of irritants *ab extra* inciting tumour germs to such proliferative activity, as may eventuate in tumour growth.

No one has, indeed, ever succeeded in intentionally producing any kind of tumour by such extrinsic agencies; although, by means of this kind, as we have already seen, somatic cells may be incited to proliferation, which sometimes results in the formation of tumour-like pseudoplasms of malignant aspect, of which I shall have more to say in the sequel. Among such extrinsic agents, microbes and their toxins hold an important place.

I cannot, therefore, concur with Ziegler,[1] when he says: "All the biological characters of tumours testify against their parasitic origin." My objection to the doctrine of extrinsic tumour pathogenesis is rather based upon the fact, that the balance of available evidence, on consideration of the *ensemble* of the subject, seems to be decidedly against it. Moreover, as the phenomena of the disease can be so much better explained without invoking the aid of this hypothesis, as a primary ætiological factor, it seems to me that we ought to leave it aside, until much stronger evidence in its favour is forthcoming than any at present available. The need for so doing becomes all the more obvious when we recollect, as in the course of my narrative I shall proceed to show, that of the many pathologists who claim to have discovered the cancer parasite, all are in disaccord as to its nature; thus, it has been ascribed to bacteria of many different kinds, to various protozoan parasites, to diverse kinds of fungi, and various other lowly parasites and pseudo-parasites. The truth is, most pathologists are so strongly prepossessed in favour of the conception that nearly all diseases, not obviously due to some gross external cause, must be of parasitic origin, that it is difficult to get them to regard this malady from any other standpoint. Hence, although the microbe of cancer has not yet been discovered, the microbic theory is still the order of the day.

Of course, the mere fact that no specific cancer microbe has yet been discovered, does not *per se* prove its non-existence for, of many maladies

[1] *Münch. med. Woch.*, 1898, Bd. xlv., S. 312.

almost certainly parasitic (*e.g.*, small-pox, vaccinia, measles, scarlet fever, syphilis etc.), the same may be said; and, as is within the recollection of every one, the microbe of tubercle was only discovered in 1882.

Neither can the absence of contagion *per se* be regarded as proof of the non-existence of a cancer microbe; for some maladies, although demonstrably of parasitic origin, are not transmissible by ordinary contagion (*e.g.*, malaria, coccidial disease of rabbits etc.).

One of the most remarkable properties of malignant tumours, is their power of continuous autonomous growth and development (individuality), upon which their so-called parasitism depends. It is by virtue of this property that they persist, and tend to increase indefinitely. Inflammatory pseudo-plasms, on the other hand, after a time tend to disappear; nevertheless, there are exceptions, for some pseudo-plasms, such as *mycosis fungoides*, as well as certain tuberculous, actinomycetic, syphilitic and some other pseudo-plasms, are often very persistent.

A striking feature about cancerous growths, is the great morphological difference that obtains between them, according to the localities whence they originate. What, for instance, can be more divergent in this respect, than the appearances presented on microscopical examination, by sections of cancer from such different parts as the breast, the stomach, and the skin? We learn from such examinations, that cancerous growths are sufficiently organized, to present unmistakable histological resemblance to the structures whence they originate. Herein they differ from most inflammatory pseudo-plasms, which present the same granulomatous structure, no matter in what part of the body they arise. When, however, epithelial elements are included in proliferating granulomatous tissue, they are often thereby incited to grow and proliferate, of which "Jensen's tumour" is an example in mice; and, in humanity—among many such instances—uterine "erosions" may be cited.

The great resemblance always noticeable between primary and secondary cancerous growths is a phenomenon of similar import, which cannot be accounted for on the basis of inflammation and micro-organisms. It is impossible to conceive a valid explanation of such conditions, without the presence of cells capable of reproducing their like by growth, multiplication, and organization. I am aware that microbists make light of this objection, alleging that the emigrant cancer cells carry their parasites with them to their new habitat, where the said parasites cause a repetition of the initial morbid process. But, independently of the fact that cells invaded by parasites tend to lose their power of growth and proliferation, it never seems to have occurred to the authors of this suggestion, how unlikely it would be for microbes transported, for instance, into the liver, to produce in this organ the typical structure of breast cancer. Surely, if the secondary lesions were really due to microbes, these might be expected to incite the liver cells to malignant growth; and so to cause the formation of typical hepatic cancer. As Moxon has sagely remarked: "The first cancer which appears has a likeness to the part in which it appears, and the secondary cancers arising from it have the likeness of that first cancer; and, those that doubt that they came from that first cancer, must show us why they have that likeness." In this connexion, Waring's[1] experiments are of interest, for they show that the cellular elements of the secondary, as well as those of the primary growths, in cancer of the pancreas and stomach, produce the same ferments etc., as the normal secretory cells of these parts.

Thus may be explained the great resemblance always noticeable between the primary and secondary growths, the significance of which it is impossible to ignore. In short, these phenomena clearly imply that the disease centres in the tumour cells themselves; and not in any extraneous condition. Thus, this peculiarity of malignant tumours, marks them off from microbic pseudo-plasms, more definitely than any other single item.

In like manner, the peculiar age and sex incidence of the malady, and the occurrence of congenital cases, testify against its parasitic origin.

Such then are some of the reasons for regarding the microbic theory of cancer as improbable.

Before a disease can properly be called parasitic, the parasite must be found, isolated; and, the disease it is alleged to cause, must be reproduced by its inoculation. Judged by this standard, the microbe of cancer has not yet been discovered; for, none of the bodies hitherto described as such, comply with these requirements. Of the numerous researches undertaken during the last quarter of a century with a view to finding it, all have proved abortive. Where now are the specific cancer microbes of Rappin, Freire, Scheuerlen, Schill, Francke, Lampiàzi-Rubino, Sanarelli, Kübasoff and Doyen; of Pfeiffer, Thoma, Wickham, Sjöbring, Soudakewitch, Ruffer, Walker, Plimmer, Adamkiewicz, Korotneff, Juergens, Bosc, Leyden and Schaudinn, Schüller, Gaylord, Feinberg, Robertson and Wade; of Russell, Sanfelice, Niessen, Bra, Monsarrat, Leopold, O. Schmidt etc.? One after another, the alleged discoveries of this recalcitrant organism, have ended only in disappointment. The negative results of numerous implantation and other similar experiments, as previously detailed, point to the same conclusion.

In short, the evidence hitherto adduced as to the existence of a specific cancer microbe, is altogether inconclusive; hence, if there really is any microbe, from whose presence in the body cancer must necessarily result, I can only conclude that it altogether transcends present experience.

As soon as the microscope had revealed to pathologists the wonders of the infinitely minute, the medical world expected that some definite morphological element would soon be found distinctive of cancer. The search for specific cancer elements, although discouraged by J. Müller and Virchow, was keenly pursued by others; and Lebert soon announced that he had discovered the specific cancer cell. When this claim proved untenable, the turn of the nucleus came and its mode of division (mitosis); while lately, as we have already seen, the centrosome has been similarly regarded. The minutest cytological investigations having, however, failed to reveal the long-expected specific element of cancer; and, chemical researches in this direction having proved equally futile, it remained for

[1] *Journal of Anatomy*, October, 1893, p. 142.

the microbists to complete the search. It is to this popular demand for a *materies morbi*, to this desire for some tangible and concrete—if empirical—explanation of the phenomena of malignancy, that the microbic theory of cancer really owes its vogue. Limited to non-malignant tumours, it would probably have gained but few adherents; hence the battle as to its relevancy, has centred round the pathogenesis of malignant tumours.

These the microbic theory regards as the product of "chronic inflammation," consequent on "irritation," resulting from the presence in the tissues, or in the cells, of living organisms or their toxins. It attributes not only the initiation of the abnormal growth, to parasitic activity; but also its progress and continuance. Thus regarded, malignant tumours would be classed with the infective granulomata.

Thus the conception of the microbists as to cancer genesis, is an exact reproduction of the doctrine of Broussais, so extensively held at the beginning of the last century, plus microbes.

It is presumed that the special action of the parasites in causing malignancy, is mainly due to the fact that they often penetrate into the constituent cells of the tumour and dwell there, as it were in symbiosis—the union being so intimate that as the parasite proliferates, so also does the nucleus of its epithelial host. It is, however, a remarkable fact—which none of those who have investigated the subject have yet explained—that the nucleus of a cancer cell invaded by "parasites," always appears to be in a state of degenerative, rather than of proliferative, activity. It accords with this, that these "parasite-containing" cells are very inapt at proliferation, or do not proliferate at all.

As to the life-history of this hypothetical parasite, nothing is yet known; but, on *a priori* grounds, it is presumed to have some analogy with that of the tubercle bacillus etc., beginning with a primary lesion at the site of inoculation, and being followed by generalization. Metchnikoff, however, maintains that it should be classed with the miasmatic diseases, and that—like malaria—it is probably propagated by spores formed outside the body, the incubation period varying from a few days to a few years.

In order to test the validity of such statements, investigators have for some time been very busy in endeavouring to discriminate and isolate these supposed parasites; to get pure cultures of them; and by inoculation to reproduce the disease in animals, afterwards recovering the "parasites" from the latter. Such is the aim of all recent researches on this question.

It is necessary to insist on the rigid enforcement of these precautions before arriving at any definite conclusions; for only thus can we avoid being deceived, by what Pasteur calls the besetting weakness of medical investigators, viz., their unfortunate tendency to generalize by anticipation.

As Crookshank says: "It is of very little value merely to detect or artificially to cultivate a microbe associated with disease. We must endeavour to establish its exact relationship with the morbid process; and the determination of the true pathogenic value of a microbe is beset with many fallacies." In the sequel, the necessity for regarding this word of caution will be abundantly manifest.

It is a well-recognized rule in pathology—although more honoured in the breach than in the observance—that familiarity with the minute anatomy of a part and of its various morbid variations, should precede the special study of any supposed pathological novelty.

It must be confessed that the original investigators of the so-called parasites of cancer entered on their quest, very badly equipped in this respect. They came armed with novelties—with new microscopes of unprecedented magnifying power, with new stains of great complexity, and with new technique of equal elaboration. Instead of first testing these inventions on normal tissues, on known morbid conditions, and on known microbic diseases, they rushed straight away to the study of the minute anatomy of cancer—a disease that had never before been investigated with this degree of elaboration. Although manifesting unfamiliarity with the latest findings in normal cytology, they never hesitated as to the interpretation of the most obscure and complicated appearances in cancer cytology. As to their acquaintance with the life-history and histological appearances of microbes, well—not to put too fine a point upon it—this, as a rule, evidently left much to be desired. Approaching a subject of this degree of complexity, thus imperfectly equipped, the need for control experiments was sufficiently obvious; yet, as the published reports show, such experiments were seldom made. If, under these circumstances, the strange sights thus brought to light in this *terra incognita* were often misinterpreted, what wonder? The hunt for "cancer parasites" has rightly been stigmatized by Schaudinn, as one of the most melancholy chapters in biological investigation; hence, in dealing with this kind of publication, we must never forget the need for criticism.

Passing now to the dominant object of the present chapter, which is to review the work done as to the "parastiology" of cancer, it may at the outset be mentioned, that microbes first began to be heard of in this connexion early in the seventies of the nineteenth century.

But, long before this, as previously mentioned,[1] similar views had been prevalent. At a later period, in the eighteenth century, cancer was regarded by John Hunter as the product of a morbid poison, which either arose spontaneously or was derived from the contagion of similar disease; and he compared it with small-pox, tubercle, syphilis, and similar diseases.

In 1809, cancer was described by R. Carmichael[2] as: "A parasitic disease due to animalculæ produced by *generatio equivoca*." He thought that carbonate of iron cured the disease, by destroying the animalculæ.

## Bacteria.

In the modern revival, it was among the schizomycetes that specific cancer microbes were first alleged to have been discovered.

Even as early as 1880, Nepveu[3] had described the presence of bac-

[1] Chapter VIII.

[2] An essay on the effects of Carbonate and other preparation of Iron on Cancer, etc. Dublin, 1809.

[3] *Gaz. Hebd. de Méd.*, etc., 1888, p. 278; also *C. R. Soc. de Biol.*, 1887, t. iv., p. 756.

teria in tumours of this kind; and Lebard[1] again called attention to this subject in 1885.

Rappin[2] in 1886, and Schill[3] in 1887, demonstrated the existence of diplococci in carcinomatous and sarcomatous neoplasms; and claimed that these were the cause of the disease.

They soon had numerous imitators in Francke,[4] Scheuerlen,[5] Freire,[6] Lampiàzi-Rubino,[7] Sanarelli,[8] Kübasoff,[9] and others. As, however, none of them really succeeded in reproducing the disease by inoculation with pure cultures, the futility of their claims for ætiological specificity soon became apparent; and they have since been entirely abandoned, and have now passed out of recollection.

At the time of its publication in 1887, however, Scheuerlen's pronouncement made a great stir. He claimed to have solved the cancer problem by the discovery of a specific bacillus, and to have reproduced the disease in animals by inoculating them with pure cultures of it. His method was that of cultivating the substance of mammary cancers upon solid media, comprising sterilized ascitic and hydrocele fluids. On the third day, a growth—in the form of a colourless film, becoming yellowish later—usually appeared, which the microscope showed to consist of short bacilli and spores. The latter—which stained readily with ordinary reagents—he often found in the dried juice of cancers; the former, he could not demonstrate in stained histological sections, but he found them in fresh cancer-juice. Bitches inoculated in the mammary region with pure cultures of these bacilli, developed there in the course of a fortnight tumours the size of a walnut. When the animals were killed—a month after inoculation—these tumours were found to be epithelial new formations, in which the spores of the bacilli could be easily distinguished.

Senger,[10] Baumgarten[11] and others, investigating Scheuerlen's bacillus shortly afterwards, showed that it was nothing but a potato bacillus, one of the several kinds of organism that grow readily on slices of potato. It was therefore a mere epiphyte, having no ætiological relation to malignant disease.

Shattock and Ballance,[12] attempting to get cultures from fragments of fresh non-ulcerated mammary cancers, removed with aseptic precautions and carefully transferred to tubes of beef peptone jelly, beef peptone agar-agar, and solidified blood-serum, concluded—since no growth took place in any of the tubes—that these tumours contained no microbes capable of cultivation. Similar experiments with sarcomatous and

[1] *Arch. Gén. de Méd.*, 1885, t. i., p. 413.
[2] "Recherches sur l'étiologie des tumeurs malignes," Nantes, 1887.
[3] *Deutsche med. Woch.*, 1887, S. 1034.
[4] *Münch. med. Woch.*, 1887, No. 4.
[5] *Deutsche med. Woch.*, 1887, No. 48, S. 1033.
[6] *Rev. d. Cursos. Prat. e. Theor. d. Fac. d. Med. d. Rio de Janeiro*, 1889, p. 73.
[7] *La Riforma Med.*, Napoli, 1888, vol. iv., p. 20.
[8] *Ibid.*, Roma, 1889, p. 356.
[9] *Wien. med. Presse*, 1890, Bd. 31, Nos. 29 to 33.
[10] *Berlin. klin. Woch.*, 1888, No. 10, S. 185.
[11] *Cent. f. Bakt.*, etc., 1888, Bd. iii., S. 397.
[12] Transactions of the Pathological Society, London, 1887, vol. xxxviii., p. 412; also *ibid.*, 1888, vol. xxxix., p. 409.

lipomatous tumours, gave the same negative results. Moreover, they found that fragments of malignant and other tumours, aseptically treated, could easily be kept sterile for considerable periods, just as could bits of the healthy tissues.

Verneuil,[1] having noticed the frequency with which his operation wounds became septically infected, after the removal of cancerous tumours in which there were areas of softening, made special bacteriological examination of these foci ; and found that they teemed with various kinds of bacilli and micrococci, several species often being present in the same tumour.

In the same year, Zahn[2]—by cultivation experiments—showed that bacteria may abound in the metastases of cancer, even when the latter have no direct communication with the surface of the body.

Hauser[3] thinks we need not be surprised to find bacteria in ulcerated malignant growths ; since, under these circumstances, the conditions met with are highly favourable to their growth and development. When microbes are found in metastatic growths, Hauser believes that they are carried there, by tumour elements detached from the primary focus.

Kübasoff[4] in carcinomata of the stomach found short, thick bacilli, which showed active movements when incubated. In various culture media—such as gelatin, agar-agar etc.—they formed scale-like colonies, which did not liquefy gelatin. Guinea-pigs, rabbits, cats and dogs, when inoculated with pure cultures, died in a comparatively short time. On post-mortem examination nodular tumours—which are described by Kübasoff as presenting the structure of cancer—were found in various internal organs. He regarded this bacillus as the true cause of the disease.

Schütz,[5] by means of various aniline dyes, was able to discriminate various forms of bacteria in ulcerated cancer of the lip ; but these he regarded as mere epiphytes.

Richet[6] found septic bacteria often present in cutaneous carcinomata ; and extracts made from tumours of this kind seemed to possess a special virulence of their own. Thus, while injections of the extract of fresh non-ulcerated cancers had no toxic effect whatever on animals, a few cubic centimetres of the same preparation from an ulcerating cancer, caused convulsions and death.

Several investigators have reported the existence of bacteria in the blood of patients with malignant tumours ; and some have claimed for these bodies special ætiological significance.

Hayem,[7] however, who has specially studied the various alterations in the form of the blood-corpuscles in malignant and other diseases, concludes that the pseudo-parasitic bodies are due to degenerative corpuscular changes (microcytosis, poikilocytosis, fragmentation etc.).

[1] *Rev. de Chir.*, 1889, t. ix., p. 793.
[2] *Arch. f. path. Anat.*, 1889, Bd. cxvii., S. 209.
[3] " Des cylinder Epitheliom des Magens " etc., Jena, 1890.
[4] *Wien. med. Presse*, 1890, Bd. xxxi., S. 1145 *et seq.*
[5] *Cent. f. Bakt.*, etc., 1890, Bd. ix., No. 21, S. 702.
[6] *C. R. de l'Acad. des Sci.*, 1895, ii., No. 17.
[7] " Du Sang," Paris, 1889.

Moty [1] found micrococci in the blood of nearly all the patients with sarcoma, examined *ad hoc* by him. In cultures they developed as a narrow, pointed or festooned band, surrounded by small isolated colonies.

Maragliano [2] examined the blood of thirty-three patients with cancer of various parts of the body. In nine cases bacteria were present—mostly different kinds of staphylococci. In all these instances, the tumours showed some signs of disintegrative processes; but, in none of the patients was there any pyrexia, or other indication of septic infection. In patients with non-ulcerated tumours, he was never able to detect any bacteria in the blood.

The latest champion of the bacterial origin of cancer is Doyen, of Paris; who, at a meeting of the French Academy of Medicine, held in December, 1901, announced the discovery of a new "cancer microbe," which he called *Micrococcus neoformans*. He maintains that this microbe—which is a diplococcus—is constantly present in cancerous tumours, and may be best demonstrated in sections stained with picro-carmine and violet; and that he has been able to isolate it, and cultivate it, in special gelatin-bouillon media. It presented in pairs, and in short chains. He found that cultures were more easily obtained from affected lymph-glands and secondary growths, than from the primary tumour. He claims to have produced cancerous tumours in various animals, by inoculating them with pure cultures of the microbe; and also to have succeeded in preparing a sterilized solution of its toxins—attenuated in a special manner—which, when subcutaneously injected into those affected with the disease, retards its progress.

In a subsequent publication,[3] Doyen claims with this solution, up to September 30, 1904, to have completely cured 42 out of 242 patients treated, and to have markedly benefited many others.

A committee of the Société de Chirurgie, which was subsequently appointed to report on Doyen's therapeutic methods and results, has lately issued an adverse report [4]—the unanimous conclusion being, that the treatment has no favourable action on cancer: "During the five months in which we have examined all the cases which M. Doyen wished to show us, we have not seen a single instance of amelioration."

Jacobs and Geets [5] have since published experiences, which tend to support Doyen's thesis; but Wright and others, who have repeated their experiments, have failed to verify their results.

### General Conclusions as to Bacteria.

From such items as the foregoing, the following conclusions may be drawn:—

1. Malignant tumours are singularly prone to bacterial infection, owing to their feeble vitality, which is a consequence of defective sanguini-

[1] *Bull. Méd.*, October 14, 1894. [2] *Gaz. degli Ospitali*, January 13, 1901.
[3] "Étiologie et Traitement du Cancer," Paris, 1904.
[4] *C. R. Soc. de Chir.*, July 12, 1905. [5] *C. R. Roy. Acad. de Méd. Belgique*, 1906.

fication. The organisms usually present under these circumstances, are such as may be commonly met with in corresponding normal parts of the body, *e.g.*, micrococci, diplococci, streptococci, staphylococci, various large and small rod-shaped bacilli etc.

2. In their young and nascent condition, non-ulcerated malignant tumours are quite free from bacteria.

3. Although many kinds of bacteria may find a suitable habitat in malignant tumours, none of these organisms fulfil the requirements necessary for the establishment of their ætiological specificity, as "cancer microbes."

## Protozoa.

Just as the movement in support of the bacterial origin of malignant tumours was on the wane, a new movement arose ascribing the causation of the disease to parasitic protozoa.

More than half a century previously, Hake [1] had noticed that cancer cells often contained certain rounded, hyaline, spore-like bodies, which he regarded as psorospermial parasites. Some years later, Virchow [2] also examined these bodies; but he concluded that they were the outcome of endogenous cell formation and degenerative changes.

About the year 1889, several cytologists (Pfeiffer, Thoma and Darier) announced that they had discovered similar bodies—which they regarded as psorospermial parasites—in cancer cells from various parts of the body. Thus the old controversy, as to the significance of these bodies, was revived; and this question soon became the cynosure of pathological eyes, for the problem of the origin of cancer seemed to concentre in it.

It appears that Pfeiffer,[3] who had specially studied coccidiosis in the rabbit, was one of the earliest to publish an account of parasitic sporozoa in human cancer. On teasing fragments of a malignant melanotic tumour, on the warm stage of a powerful microscope, he saw plasmodia in amœboid movement; and observed that they resembled one of the microsporidia, which infest the roots of cabbages and other cruciferæ—the *Plasmodiophora brassicæ*.

At about the same time Thoma [4] described certain endocytes, which he found in the protoplasm and nucleus of cancer cells; and he maintained that they were coccidia.

The announcement by Darier [5] in the same year, of the discovery of coccidial parasites in cases of "Paget's disease" of the breast, contributed not a little to the general interest which the subject had excited.

Among the earliest supporters of the protozoan origin of these endocytes, besides those above mentioned, were Malassez, Albarran, Wickham, Metchnikoff, Soudakevitch, Ruffer, Foà and Cattle; while their non-parasitic nature was just as strenuously upheld by Borrel, Cornil, Gibbes, Klebs, Ribbert, Pianese, Delépine, Sroebe, Virchow, Kanthack and others.

[1] "A Treatise on Varicose Capillaries," etc., London, 1839.
[2] *Arch. f. path. Anat.*, Bd. i., SS. 107, 130, 483; also Bd. iii., S. 197.
[3] "Die Protozoen als Krankheitserreger," Jena, 1891.
[4] *Fortschritte der Med.*, 1889, Bd. vii., S. 413.
[5] *C. R. Soc. de Biologie*, April 13, 1889.

The work of these early investigators was entirely histological; and, it soon became apparent, that they meant to class as cancer parasites, every rounded body that was not obviously either an epithelial cell, a nucleus, a leucocyte, or a red blood-globule. Indeed, there were some among them (Pfeiffer, Adamkiewicz, Jackson Clarke etc.), who went to much greater lengths, maintaining that the constituent elements of cancerous tumours were merely masses of parasitic protozoa; and, not epithelial cells, as generally believed. In spite of some opposition from the more moderate parasitologists, the investigation was continued in this spirit, until Soudakevitch[1] and Ruffer[2] for the first time clearly defined precisely what was meant by the term "cancer parasite." They thus discriminated from the immense variety of so-called parasites, certain small, rounded endocytes, each of which contained a nucleus, surrounded by voluminous protoplasm, itself circumscribed by a distinct capsule. With the Ehrlich-Biondi stain the nucleus assumed a copper-red colour, while the surrounding protoplasm coloured light greenish or bluish, the capsule taking a decided reddish tint. Immediately around the nucleus a clear zone was noticeable; and, in "parasites" of a certain size, fine radial striation was often seen. All bodies different from these, such as had been described by previous observers as cancer parasites, Ruffer rejected as such, declaring that they were only pseudo-parasites, having no ætiological relationship whatever with malignancy.

The precise nature and significance of the bodies thus discriminated, still remain to be determined. Shattock and Ballance[3] were among the earliest of those who undertook experiments, with the object of determining whether cancer could be produced by inoculating animals with psorospermiæ from the rabbit's liver etc., as the statements of Darier and Wickham implied. Rabbits, monkeys, dogs and rats, were employed for this purpose. The method was to scarify the ear, by making one or more long incisions on its inner aspect; and, after bleeding had ceased, to rub into the wounds fresh psorospermial material from the liver of a recently killed rabbit. This was followed by the formation of linear elevations along the incision tracks, owing to reparative hyperplasia; but, otherwise, the results were always negative. This was the case, even when large quantities of psorospermial material were injected into the jugular vein of dogs etc.

They concluded that, until animals or human beings had been experimentally infected by inoculation, with cultures made from Paget's disease or from cancerous tumours, nothing could be taken as proved, as to there being any causal relation between psorospermiæ and cancer.

According to Adamkiewicz,[4] the infectivity of cancer is so well established, that its parasitic nature may be regarded as a certainty. He maintains that the constituent cells of cancerous tumours are not epithelial cells, as is generally believed, but parasitic organisms. "A cancer cell is not an epithelial cell, but an animal—a protozoön—especially a coccidium (*Coccidium sarcolytes*)." Since all parasitic microbes produce

[1] *Ann. de l'Inst. Pasteur,* 1892, No. 3, p. 145; also *ibid.*, No. 8, 1892, p. 545.
[2] Transactions of the Pathological Society, London, 1893, vol. xliv., p. 209.
[3] *Ibid.*, 1891, vol. xlii., p. 377.
[4] "Untersuchungen über den Krebs," Wien, 1893, etc.

toxins, Adamkiewicz believes that there must also be a special cancer toxin; and this he claims to have discovered in a substance, termed by him "cancroin," which he has extracted from malignant tumours. He finds that this substance is chemically akin to neurin—"tri-methyl-vinyl-ammonium-hydroxide."

By implanting brain substance and other tissues from cancer patients, into divers regions of various animals, Adamkiewicz claims to have caused in them a specialized intoxication, owing to the action of this toxin. No cultures of any parasitic organism were made.

Geissler, Kopfstein and others, who repeated these experiments, were unable to confirm Adamkiewicz's results.

By subcutaneously injecting cancer patients with cancroin, Adamkiewicz also claims to have cured many, even after only a few weeks' treatment. It must be stated, however, that those who have had the best opportunities of closely following his cases, have failed to appreciate his alleged curative results; and, generally, his statements inspire no confidence.

Delépine[1] found that the psorospermia-like bodies met with in malignant tumours failed to respond to any of the chemical tests, which give definite reactions with the psorospermial parasites of the rabbit's liver. He also failed to find in the so-called "cancer parasites," any of the developmental forms met with in the parasitic psorospermiæ of rabbits.

By inoculating interlamellar films of water, serum, nutrient gelatin, and other fluids, with psorospermiæ from the rabbit's liver, he obtained cultures of these parasites, and succeeded in following their development through various stages. By this method, the changes occurring in individual psorospermiæ could be followed for weeks.

Delépine suggests that the protozoa-like bodies of malignant tumours, should be studied in the same way; when, if similar changes were observed in them, the doubts as to their real nature might thus be removed. Attempts subsequently made in this direction by Delépine and Cooper, failed to elicit any indications of multiplication and growth when the so-called cancer parasites were substituted, in the experiments, for psorospermiæ from the rabbit's liver.

D'Arcy Power,[2] a supporter of the protozoan theory, has also attacked the problem from an experimental standpoint. He brought mucous surfaces—of rabbits rats, etc.—that had for some time been kept in a state of chronic irritation, into contact with cancerous tissues, when the former became infected with "cancer bodies"; but, cancerous tumours could never be thus produced. Only a few experiments were made; and there were no control observations with healthy epithelial, instead of cancerous tissues, so that these results are by no means convincing.

In a subsequent publication (1894), Power admits the validity of this criticism; for, he there says: "It may be that the "cancer bodies" are merely phases in the degeneration of cells. . . . They are met with in normal epithelium, which has been slightly irritated; and, I am there-

[1] Transactions of the Pathological Society, London, 1891, vol. xlii., p. 371.
[2] *British Medical Journal*, 1893, vol. ii., p. 832; also *ibid.*, 1894, vol. ii., p. 638.

fore bound to confess myself an unbeliever, in any of the "cancer bodies" which have yet been discovered."

Kurloff[1] found an organism, which appeared to be identical with the *Rhopalocephalus canceromatosus* of Korotneff, in a primary cancer of the skin of the dorsum of the hand of a man aged eighty.

In a further series of experiments, Shattock and Ballance[2] again endeavoured to get cultures of the "parasitic protozoa" of human malignant tumours. Under the impression that it might be necessary for the hypothetical parasites to pass through some lower organism, in order to acquire infective properties for man and animals, they fed worms, kept in sterilized sand and water, with bits of mammary cancer. These were devoured, but the worms unfortunately died soon afterwards, owing to the sterility of the sand depriving them of all other nutriment. Bits of fresh mammary cancer were next buried in garden soil, and six weeks later these were exhumed and introduced into the abdominal cavity of rats; but only negative results ensued. In other experiments, fragments of malignant tumours in Petri dishes etc., were introduced into sterilized sand and water to which a little beef peptone broth had been added: after variable periods, sand from the vicinity of these bits of buried tumour was examined; but, although the sand often teemed with amœbæ and bacteria, no sporozoa were present. The results of inoculating animals with this sand, and with bits of the tumours that had been buried, were always negative.

Searching for a protective vaccine against malignant disease, Shattock and Ballance tried the effect of subcutaneous injections of 50 per cent. glycerine extracts of cancer and sarcoma, into patients affected with inoperable malignant tumours; but in no case did any improvement ensue.

They next essayed the effect of injections of the fresh serum of animals, such as sheep, which are naturally but little liable to malignant tumours; but these also were inefficacious. The serum of animals into whose circulation cancer-juice had been injected, was also employed therapeutically; but without any appreciable result.

Bosc[3] endeavoured to get cultures of the hypothetical psorosperms of human cancers, by incubating bits of recently removed tumours in ordinary culture media. He maintains that the "cancer bodies" multiplied in these media; but, as he never even attempted to inoculate animals with the cultures, the value of his statements is comparatively small.

Among those who continued the investigation of the "cancer parasites" discriminated by Soudakevitch and Ruffer, Plimmer[4] was one of the first who employed the experimental methods, that had been introduced by Sanfelice and the Italian pathologists. He seems to have been so much impressed by the results of these methods, as even to doubt the dictum of Metchnikoff, as to the protozoan nature of these bodies.

Although Plimmer managed to demonstrate histologically to his

[1] *Cent. f. Bakt.*, etc., Bd. xv., Nos. 10 and 11.
[2] Proceedings of the Royal Society, 1895, vol. lix.
[3] "Le Cancer," Paris, 1898.
[4] Proceedings of the Royal Society, March 9, 1899; also *Practitioner*, April, 1899.

satisfaction " cancer parasites " in almost all of the numerous malignant tumours specially examined *ad hoc*, he only once succeeded in isolating by artificial culture " an organism which in certain animals was capable of causing death, with the production of tumours in various parts." His culture medium was an infusion of human cancer prepared, just as the ordinary beef infusion, with the addition, after neutralization, of 2 per cent. of glucose and 1 per cent. of tartaric acid.

Guinea-pigs inoculated intra-peritoneally with these cultures, died in from thirteen to twenty days; and on post-mortem examination the peritoneum, omentum, liver, spleen, intestines and lungs, were found to be studded with small nodules of endothelial structure, the constituent cells of which contained " organisms " similar to those isolated from the human cancer. He claims that these experiments demonstrate " the production of tumours by an organism isolated from human cancer "; which, he thinks, " may have a practical bearing on the great question of the ætiology of cancer." In some cases he claims to have produced by inoculation, true malignant epithelial (cancerous) tumours. Thus, by scarifying a rabbit's cornea, and inoculating it with the sediment of a ten-days-old culture, he found, when the animal was killed forty-eight hours afterwards, that free proliferation of the corneal epithelium had taken place, and that these cells were invaded by " cancer parasites." This proliferation spread for some distance. Plimmer believed that this was an artificially produced cancerous lesion. I certainly think that he has not brought forward one iota of evidence, that will justify such a conclusion. This lesion might just as well have been produced by the inoculation of any irritant. Wyss and others have shown that corneal lesions of all kinds, involving destruction of surface epithelium, are quickly followed by ingrowths of the adjacent epithelial cells, with histological appearances like cancer.

In numerous other experiments, rabbits and guinea-pigs were inoculated intra-venously, intra-peritoneally, and subcutaneously; but with merely negative results. In yet other cases, the only obvious effect was; that the " organisms " were found post-mortem in the blood, internal organs etc.

Pianese[1] has published a very elaborate study of the cytology of cancer, with special reference to the nuclear changes of the morbid cells, and to the so-called parasites. He examined specimens from fifty-five cancers of different parts of the body. He describes the mitoses found in cancers, which he classifies. Special attention is given to the group of degenerations which comprises hyalinosis, keratohyalosis, mucoid, colloid, and amyloid changes; and their relations to *les corps de Darier*, the sporozoa of Korotneff (*Rhopalocephalus canceromatosus*), and to Russell's bodies. Endocytes due to secretory changes in glandular cancers are also studied.

Attention is then directed to the nucleus and nucleolus of cancer cells; for, having found that chromatin often occurred in these inclusions, Pianese maintained that many of them had a nuclear origin. The

[1] " Beitr. z. Histologie und Aetiologie des Carcinoms " (suppl. *Ziegler's Beitr. z. path. Anat.*, Jena, 1896).

special nuclear changes may affect chiefly (*a*) the nuclein (swelling, diminution, fragmentation, degeneration); (*b*) the paranuclein (fragmentation, degeneration); or the nucleolus (vacuolization, encapsulation); (*c*) the envelope of the nucleus; or (*d*) the nuclear juice (filamentous, nucleoplasmolysis).

In conclusion, he studied :—(1) hyalinosis of the nucleoplasm; (2) pseud-adipose or cystic degeneration of the nucleus; (3) amyloid degeneration of the entire cancerous cell; (4) necrosis of the nucleus; and (5) amyloid cancer bodies.

Pianese concludes that, up to the date of his communication (1896), we had no evidence, histological or experimental, that would justify us in describing any of the numerous "parasites," such as have been figured and described as being found in cancers, as other than products of alterations of the protoplasm, of the nucleus, or of both combined.

Leyden and Schaudinn,[1] examining ascitic fluid removed from cancer patients, made the interesting discovery, that it teemed with rhizopodia —organisms that had never before been met with in the human body, except as parasites of the gastro-intestinal tract. These microbes presented as amœboid bodies, of from 3 to 36 millimetres in diameter, their shape being globular or irregularly polygonal, and having a characteristic appearance, which is compared to a bird's eye. At intervals they emitted processes of hyaline ectoplasm, and the pseudo-podia of adjacent organisms sometimes anastomosed. Each of them was furnished with a nucleus of the typical rhizopod type; and they multiplied by segmentation or gemmation, colonies often being formed. One of the patients above referred to had cancer of the pylorus; the other had an intra-abdominal tumour.

When a drop of the ascitic fluid or its centrifugalized sediment, was microscopically examined in the fresh state, the organisms were readily seen, as above described. Permanent preparations were also made. As to the possible ætiological relation between these rhizopods and the concomitant cancerous disease, the authors at first declined to commit themselves; but they subsequently affirmed their belief that the organism is the specific cancer parasite, although they were unable to comply with Koch's postulates; and they have named it *Leydenia gemmipara Schaudinn.*

The foregoing publication has been the starting-point of many subsequent researches. Thus Nils Sjöbring,[2] with a culture medium consisting of nearly equal parts of sterile ascitic fluid and peptone gelatin, with the addition of 1·5 per cent. of watery solution of potash soap prepared with human fat, and 1 per cent. of cane- or grape-sugar, succeeded in cultivating—from fresh human tumours—an animal organism presenting amœboid, rhizopod, and involution forms.

Tubes of this special culture medium were inoculated with pieces of non-ulcerating human tumours, that had been aseptically treated; and these were then incubated for a week at 37° C. (98·6° F.). By this

[1] "Sitz. d. Akad. d. Wissenschaft z. Berlin," 1896, Bd. xxxix., S. 13; also "Über die parasitäre Theorie in der Aetologie der Krebse," Berlin, 1905.
[2] *Fortschritte der Med.*, 1890, No. 14; also *Cent. f. Bakt.*, etc., 1900, xxvii., S. 129.

means, from various carcinomata, sarcomata, uterine myomata, and ovarian cystomata, Sjöbring succeeded in isolating these rhizopod organisms.

With these cultures he inoculated eight white mice, and in four cases positive results were obtained. In two cases cultures of human mammary cancers, subcutaneously injected, after a period of three months, are alleged to have caused the formation of cylinder-celled cancer of the cutaneous sweat-glands and hair-follicles. In another experiment, the resultant tumour resembled an adenoma of a sweat-gland. In the fourth case, a culture from a colloid cystoma of the human ovary, intra-peritoneally injected, gave rise to colloid cystoma of the epididymis etc. In all of these animals "cancer bodies," similar to those found in human malignant tumours, were demonstrated. With rabbits and guinea-pigs the inoculations gave only negative results.

In their initial stage these "organisms" presented as sarcous, rounded, quasi-fatty masses; subsequently pseudo-plasmodia developed. In certain forms the nuclear chromatin could be demonstrated, by aniline blue staining and with iron-alum-hæmatoxylin. Their development was like that of the amœbosporoids of the protozoa; but sexual conjugation, and the sickle-shaped germ, were absent.

Histological sections of the artificially produced skin tumours in mice, exhibited at the Congress of German surgeons in 1901, produced a by no means favourable impression. The evidence as to epithelial new formation, was considered to be inconclusive. Juergens could not recognize the so-called cancer bodies as parasites; and Israel was of the same opinion, maintaining that the so-called sporophoroides and rhizopodia were nothing but fat globules and débris.

Max Schüller [1] has published an account of an organism—of protean form—which he detected in carcinomatous and sarcomatous tumours, and isolated by cultures. His procedure was that of incubating bits of the fresh tumours, taking care not to expose them to a lower temperature than that of the body. He discriminates two typical forms; of these, the more characteristic are large organisms, three or four times the size of red blood-corpuscles—round or ovoid, refractile, of golden yellow or brownish colour, having a well-defined capsule perforated by numerous pores, within which are three or four small protoplasmic masses, which, in the course of development, appear to escape through the capsular pores and form independent organisms. It is from the latter that the smaller type of organism is believed to originate; these present as clear or finely granular, rounded cells of golden colour. These small forms act as intracellular parasites, penetrating the tumour cells, even to their nuclei, where they undergo their further phases of development—identical parasites being found in both the epithelial and connective-tissue forms of malignant disease.

In living, hanging-drop cultures, these organisms present fine peripheral processes. It is believed that the small types of organism develop into the larger ones.

[1] "Die Parasiten im Krebs und Sarkom des Menschen," Jena, 1901; also abstract in *Cent. f. Bakt.*, etc., 1900, Bd. xxvii., S. 511.

Cultures injected into the tissues and organs of rabbits and other animals, caused local proliferations, similar to those met with in commencing cancer—carcinomatous cultures being capable of producing sarcomatous etc.

Max Schüller has also found and made cultures of similar organisms, from the lesions of acquired and congenital syphilis.

Not a little sensation was caused when, in 1901, Völcker[1] declared that Max Schüller's large yellow, cancer parasites, were in reality nothing but cork cells; which had got into the specimens, through the medium of the oil used for clarifying the same.

According to Hansemann,[2] the endocytes of cancer cells are derived from many different sources, which he enumerates as follows:—(1) Degenerations of cells and secretory anomalies, (2) phagocytosis, (3) invagination, (4) abortive and pathological mitoses, (5) special organs of cells, *e.g.*, archoplasm and centrosome, (6) extra-cellular hyaline drops (Russell's bodies), and (7) cancer cells themselves.

In a previous chapter I have referred to the observations of Borrel and Le Count, as to the identity of Ruffer's endocytes with the archoplasm and centrosome.

Olt[3] considers that the so-called parasites of cancer are, in reality, red blood-cells in various stages of degeneration. He attempted to obtain cultures from cancers from the horse, dog etc., using various media. The results were negative. He concludes:—"From the fact that these supposed parasites are iron-containing bodies, and that their optical properties are very similar to those of the red blood-cells, it may be inferred that the latter are concerned in their formation." Sjöbring's rhizopod parasites, Olt regards as nothing but particles of free fat.

Bruandet[4] by injecting a solution of coccidia into the pelvis of the kidney of a rabbit, after having ligatured the ureter lower down, claims to have caused thereby quasi-cancerous epithelial changes in the kidney, as determined by histological examination, when the animal was killed about three and a half weeks after the injection.

Gaylord[5] claims to have discovered "the protozoan of cancer," in ascitic fluid derived from a patient with colloid cancer of the peritoneum; which, when inoculated into animals, produced cancerous tumours. Cultures of this organism on *Fucus crispus* bouillon gave similar results. He also found microbes of this kind, in various cancerous and sarcomatous tumours; and got pure cultures of them. In advanced cases, they could always be detected in the patient's blood, and in the internal organs. With cultures from these various sources, many animals were inoculated; and, in a few instances, nodular tumours were found a month or so later, when the animals were killed. In an experiment in which the injection was made into the jugular vein of a guinea-pig, a pulmonary nodule was found, when the animal was killed three and a half weeks later. Microscopical examination of this artificially produced tumour, revealed proliferous cells in branching columns, which Gaylord interpreted

[1] *Deutsche med. Woch.*, July 25, 1901.
[2] *Berlin. klin. Woch.*, 1894, No. 1.
[3] *Deutsche thierärzt Woch.*, 1900, Nos. 22 and 23.
[4] *La Presse Méd.*, 1902, p. 400.
[5] *Journal of the American Medical Association*, 1901, vol. cxxi., p. 503.

as adeno-carcinoma. For the demonstration of this protozoön, Gaylord relies chiefly on unstained specimens—the scrapings of cancerous tumours etc. He found the parasites in every case of cancer and sarcoma specially examined, as well as in myoxma, fibro-adenoma, colloid goitre, and syphilitic glands. It is evidently very similar to the bodies previously described by Schaudinn and Sjöbring, and to Max Schüller's "young forms." In the fresh state, Gaylord's parasite closely resembled fatty gloubles; indeed, it was only by finding that they did not react with ether and osmic acid as fat does, that he was able to discriminate them from fatty aggregations. He next found, that he could crack their edges with a cover-glass. They existed in greatest abundance, in the softened disintegrating areas of cancerous tumours, where Plimmer and Ruffer could never find parasites.

Gaylord maintains that there is great resemblance between his cancer parasites; and the bodies met with by Pfeiffer and others, in variola and vaccina, which are also believed to be protozoa. They present as pale yellowish, granular bodies, like fat droplets, from 3 to 10 millimetres in diameter, large and small types being discriminated. By incubating hanging-drop preparations of fresh cancer-juice, derived from scraping the tumour, the smaller forms of the organism could be followed in their development; they augmented in size and became granular, emitting pseudo-podia and developing a nucleus, ultimately being converted into sporiferous sacs.

Feinberg [1] claims, as the outcome of histological research with special staining, to have discovered a new intra-cellular sporozoan cancer parasite (*Histosporidium carcinomatosum*), which he maintains—solely on the histological appearances—is the true cause of the disease. It is in the nucleus of this parasite, and in its staining reactions, that Feinberg finds the distinctive features requisite for the recognition of the same. Outside the body, he believes this organism only exists in the spore form.

Otto Schmidt [2] claims to have discovered a protozoön-like parasite in malignant tumours, which he has cultivated outside the body; white mice, injected with these cultures, developed malignant tumours. He has found this parasite in animal, as well as in human, malignant tumours. Dead cultures of this organism, and the serum of animals immunized by culture inoculations, were found to exert protective action against malignant growths. Schmidt also claims to have cured many persons affected with cancer, by means of similar inoculations; and greatly to have benefited still more.

This supposed cancer specific has been tested at the Middlesex Hospital; [3] but, none of the patients there treated, derived any benefit from the procedure.

It has been pointed out, that the "cancer parasites" described by Leyden, Sjöbring, Schüller, Gaylord, Feinberg and some others, much resemble the *Plasmodiophora brassicæ*, a parasitic organism, which causes tumour-like swellings (club-root) in cruciferous plants. As pre-

[1] *Wien. klin Woch.*, 1903, No. 45, S. 1235; also "Des Gewebe und die Ursache der Krebsgeschwülste," etc., 1903.

[2] "Mittheilung aus Dr. O. Schmidt's Laboratorium," 1905.

[3] *Arch. Middlesex Hospital*, 1904, vol. iii. (J. W. G. Myler).

viously mentioned, Pfeiffer, who first described the endocytes of cancer as parasitic protozoa, long ago called special attention to this similarity. This organism lives symbiotically in the infected plant-cell, its spores being found even within the nucleus; and thus it is believed that the abnormal local cell proliferation is excited, which results in the formation of the tumour-like excrescences. It is claimed that, just as these plant formations are caused by the plasmodiophoræ; so human cancers are caused by parasitic intra-cellular protozoa. To test this conception, Podvyssotski[1] has struck out a new line, by experimenting with this organism, which is a kind of myxo-myces. He inoculated rabbits, rats, guinea-pigs etc., with these parasites, producing granulomatous formations—" myxo-mycetic perithelioma," but not epithelial proliferation. Within the cells of these artificially produced tumours, he found spores of the plasmodiophora; in such vicinities there were also many giant cells, and evidences of phagocytosis. These nodular formations were, however, evanescent.

Gaylord[2] has also made experiments of this kind. Thus, with fresh " club-foot " material, various animals were inoculated; and, when these were killed on the twelfth day after the experiment, granulomatous nodules were found, which comprised many phagocytic cells, in which were spores and spore cysts. There was also some infiltration of the surrounding tissues with leucocytes. The histological appearances of these spores were often, " indistinguishable from those of cancer inclusions "; but there were no signs of epithelial proliferation, nor of any structure like cancer. According to Gaylord, these artificially produced nodules were true grafts—their cells being derived exclusively from the cells experimentally implanted.

Tuboef[3] inoculated many animals with this same parasite; but produced nothing at all like cancer.

Robertson and Wade[4] claim to have proved by histological methods, that cancerous tumours comprise intra-cellular parasites, which are identical with the *Plasmodiophora brassicæ* in its pre-spore, spore, pre-amœboid and amœboid stages; but much more minute. The reactions of these bodies with the platinum and silver-gold methods, were identical with those given by the " club-foot " parasites. They also claim to have grown from cancerous tumours, an organism which represents the post-spore or pre-amœboid stage of a plasmodiophora; and they maintain that this organism has the same relation to cancer, as the *Plasmodiophora brassicæ* has to " club-foot "; that is to say, is its specific causative factor. No inoculation experiments are reported. Altogether, the authors' conclusions seem to go beyond what is warranted by the ascertained facts. In view of the cloud of adverse witness set forth in the preceding narrative, as well as in what follows, the futility of claims to determine the nature of cancer endocytes, solely by histological methods, ought by this time to be generally recognized.

[1] *La Presse Méd.*, 1900, p. 77.
[2] Fourth Annual Report of the Cancer Laboratory, New York State Board of Health, 1902-1903, p. 20.
[3] " Verhandl. d. Komites f. Krebsforschung," S. 74, Berlin, 1902.
[4] *Lancet*, 1904, vol. ii., p. 469; also *ibid.*, 1907, vol. ii., p. 358.

In a recently published account of "further researches," the authors claim to have confirmed their previous findings; and the parasite is now identified as "*Spirochœta microgyrata.*" Thus a spirochætan origin of cancer is suggested.

As Lubarsch has well said, those who claim that these endocytes are parasites, must not only prove that they resemble known parasites; but also that they cannot be anything else. The need for insisting on the strict observance of this wholesome precaution is emphasized, by the recollection of the innumerable diverse interpretations, that have been placed on these appearances by equally competent workers; some of whom (*e.g.*, Plimmer and Sawtchenko) have even regarded the very same bodies at one time as protozoa, and at another time as blastomycetes etc.

Very thorough investigations as to the nature of the special "bird's-eye" cell inclusions, described by Soudakevitch, Ruffer and Plimmer, as typical of the protozoan cancer parasite, have lately been made by Greenough,[1] Nösske,[2] and Honda.[3] All the above are agreed that these endocytes are not parasites; but secretory products, formed in cells of glandular origin—cancerous as well as non-cancerous (*e.g.*, chronic cystic mastitis, fibro-adenoma etc.). They dispute the contention of Plimmer and Gaylord, that inclusions of this kind are met with in all malignant tumours, having found them absent in epidermoidal cancer of the skin and in sarcoma.

Blum,[4] the latest student of this matter, finds no reason for regarding these bodies as parasites; and maintains that there is no evidence to connect them, in any way, with the causation of cancer.

Of a large number of culture experiments made in various media, with cancerous tissue, O. Richardson[5] was unable to cultivate from the morbid tissues and fluids, any specific infecting organism.

### General Conclusions as to Protozoa.

Before entering on any discussion as to the ætiological significance of the hypothetical protozoa of malignant tumours, we want to be reasonably assured that such parasites really exist in these tumours. Hence, it is to this aspect of the question, that we must first of all direct our attention.

It will be gathered from what has been stated, that the evidence hitherto adduced is almost entirely histological; for, the results of so-called cultures and of inoculation experiments, in this connexion, have established nothing definite.

Even if pathologists were unanimous in interpreting the appearances revealed on microscopical examination of malignant tumours, as indica-

[1] Third Report of the Croft Cancer Commission of Harvard Medical School, 1905, p. 29.

[2] *Deutsche Zeits. f. Chir.*, 1902, Bd. lxiv., S. 352.

[3] *Arch. f. path. Anat.*, 1903, Bd. clxxiv., S. 96.

[4] *Ibid.*, 1905, Bd. clxxix., S. 475.

[5] Second Report of the Croft Cancer Commission of Harvard Medical School, 1902, p. 46.

tive of the presence of protozoa ; in the absence of corroborative evidence, such unanimity would fall far short of scientific proof. But, when we find that most pathologists decisively reject this interpretation, maintaining that the bodies which have been thus described are not parasites at all, but merely products of the biological changes—often degenerative—incidental to the life of the part, secretory products, derivatives of the nuclei or protoplasm of the tumour cells, of leucocytes, of red blood-globules etc. ; the futility of relying on the appearances revealed by the microscope, for the proof of the presence of parasitic protozoa in malignant tumours, becomes apparent.

It is passing strange, that those who are so insistent on maintaining the protozoan nature of certain appearances revealed by the histological examination of malignant tumours have, with singular unanimity, failed to make control observations. Had they done so, they would have found similar appearances often present in various non-cancerous conditions, *e.g.*, in chronic cystic mastitis, in mammary adenoma etc. (Greenough) ; in variolous and vaccinal lesions (Pfeiffer, Guarnieri, Mann etc.) ; in healing wounds, and after artificial irritation (Spirlas, Pierallini, D'Arcy Power, Galeotti etc.) ; in syphilitic lesions, herpes, endometritis, mycosis fungoides etc.

Moreover, in undoubted cases of human psorospermosis, such as those described by Leuckhart, Albarran, Keen, Silcock, Eve, and others, the lesions met with bore no resemblance whatever to malignant disease. Similarly in animals (rabbits etc.), the lesions caused by these parasites never present any of the special features of malignant tumours.

It accords with this, that tumour cells containing "parasitic protozoa" always appear to be in a state of degeneration ; and to be incapable of that active proliferation, which is an essential feature of malignancy.

Again, the chemical reactions of malignant tumours are very different from those of lesions in which psorospermia abound ; for, they contain neither chitin, cellulose, nor albumose (Brodie, Hewlett). On the other hand, they are rich in glycogen ; which, according to Brault, is absent from parasitic pseudo-plasms. Moreover, "falciform bodies" have never been demonstrated in the so-called psorospermia of malignant tumours ; and no alkaloid has ever been separated from them.

Before such bodies as those described by Schaudinn, Sjöbring, Max Schüller, Gaylord, Feinberg, Robertson and Wade, can be accepted as parasitic protozoa, the possibility of their being derivatives of pre-existing somatic structures must be negatived.

The more carefully the subject is considered, the clearer it appears ; that the "protozoön of cancer" has failed to make good its entity. This hypothetical microbe appears to be a mere figment of the imagination, which has been projected into the field of observation, in consequence of errors of diagnosis : it is a case of mistaken identity.

In this opinion, modern zoologists are at one with pathologists ; thus Doflein,[1] the latest investigator of the protozoa, says : "The zoologist cannot at present admit, that any one of the so-called cancer parasites, is a protozoön."

[1] "Die Protozoen als Parasiten und Krankheitserreger," Jena, 1901.

## Blastomycetes.

The third great movement in connexion with the microbic origin of malignant tumours was originated by Russell,[1] who (in 1890) detected certain "fuchsin bodies" in cancerous tumours, which he regarded as the characteristic organisms of cancer; and these he believed to be parasitic blastomycetes, of the same order as the yeast fungi. It cannot be said that Russell's views met with much support, until some years later, when the Italian pathologists took the matter up; and, by means of experimental methods, aroused fresh interest in the subject.

It is especially owing to the work of Sanfelice,[2] Director of the Hygienic Institute at Cagliari (Sardinia), that so much attention has centred on the blastomycetes in this connexion. Moreover, he removed the study of the subject from the histological to the experimental region. It appears that, even as early as 1895, he was engaged in studying certain organisms found in infusions of various kinds of fruits; and, in so doing, he was struck with the resemblance which some of them presented to the so-called "fuchsin" bodies, found by Russell in human cancerous neoplasms. Of these organisms he obtained pure cultures, with which he proceeded to inoculate the tissues and organs of various animals. He thus found that some of them were pathogenic, the effect varying in different animals. In many animals nodular swellings were produced at the seat of inoculation, in adjacent lymph-glands, and sometimes in more distant parts, which he thought might not unfairly be compared with human malignant tumours.

Sanfelice had no doubt that the organisms he experimented with were blastomycetes; and, the pathogenic form, he discriminated as *Saccharomyces neoformans*. In most cases, the tumours thus produced were nothing but inflammatory pseudo-plasms. But, with cultures of a microbe of this kind, isolated from a fermenting infusion of lemon-skin, he claims to have produced, by inoculation, malignant epithelial neoplasms (cancers) in dogs.

When these cultures were injected into the peritoneal cavity, nodular formations at first resulted; from these fresh cultures were made, and after the microbe had thus been passed through several dogs, it was found to have acquired increased virulence.

Of thirty dogs inoculated with cultures thus produced, in two Sanfelice claims to have caused true epithelial cancer.

In the case of a bitch inoculated in the posterior mammary region, there was considerable tumefaction at the seat of inoculation one month afterwards. The animal then became cachectic, and died ten months after inoculation. Besides the mammary tumour, post-mortem examination revealed enlargements of the adjacent inguinal and abdominal lymph-glands. Histologically examined, all of these tumours showed

[1] *British Medical Journal*, 1892, vol. ii., p. 1356.

[2] *Cent. f. Bakt.*, etc., 1895, Bd. xvii., S. 113 and 625; Bd. xviii., S. 521; Bd. xxiii., SS. 155 and 276; and Bd. xxi., 1902, S. 254. Also series of articles in *Zeits. f. Hygiene und Infections-krankheiten*, 1895, Bd. xxi., SS. 32 and 394; Bd. xxii., 1896, S. 171; Bd. xxvi., S. 298; Bd. xxix., 1898, S. 463.

the structure of glandular cancer. Numerous "parasites" were present in them, but no cultures could be obtained. The latter defect is unfortunate, as the possibility of the animal having been previously affected with mammary cancer, to which bitches are exceedingly prone, thus cannot be excluded.

A similar defect characterizes the other positive result; when, after inoculation of the testes, a secondary tumour formed in the penis. Sanfelice also claims to have isolated blastomycetes from human malignant tumours; but, when cultures of these organisms were injected into various animals, no tumour formation ensued.

In a recent publication [1] Sanfelice still claims, that he can produce malignant tumours in animals, by inoculating them with blastomycetes and their soluble products.

Roncali,[2] investigating the subject chiefly from the histological standpoint, has detected in human cancers and sarcomas intra- and extracellular bodies, similar to those described by Sanfelice. He is convinced that these bodies are parasitic blastomycetes.

With Sanfelice, in 1898, he succeeded in isolating similar organisms from human cancerous tumours, which they found to have pathogenic properties; but, when these were injected into certain animals, only pseudo-inflammatory, tumour-like swellings resulted. These cultures were made with difficulty, and they soon lost their virulence, so that nothing further was accomplished in this direction.

At the meeting of the Italian Surgical Congress, in 1900, Roncali again took up this question. He described the appearances found on histological examination, of an intra-cranial fibro-sarcoma of the dura mater. This tumour teemed with parasitic blastomycetes. After having fully described their morphological features and their precise localization in the tumour, which were such as clearly indicated genetic correlation, he arrived at the following conclusions:—(1) This case proved that blastomycetes could not be mere accidental epiphytes in malignant tumours. (2) Although he failed to isolate and cultivate blastomycetes from the tumour, this was no proof that they did not exist, nor did it imply that they were products of degeneration; for, as Sanfelice had shown, when the parasites assumed the form of "Russell's bodies," they were no longer cultivable. (3) Provided one knew how to recognize them, and had the patience to search for them, these parasites could always be found in malignant tumours. (4) The so-called parasitic protozoa and coccidia, described by other investigators as being constantly present in malignant tumours, were nothing but blastomycetes, as the author has maintained ever since 1895. (5) Blastomycetes were the real ætiological factor of malignant tumours (epithelioma and sarcoma), as Sanfelice had experimentally demonstrated.

In the interesting discussion which followed the reading of Roncali's paper, Bastianelli maintained that it was not sufficient to have stained and described these bodies, to prove that they were blastomycetes. It

[1] *Annali d'igiene sperimentali*, 1907, vol. xvii.
[2] *Il Policlinico*, October 1, 1895; and *ibid.*, October 31, 1896 (suppl.); also *Cent. f. Bakt.*, etc., 1895, Bd. xviii., Heft 12-15; *ibid.*, 1898, Bd. xxiv., Abth. i., S. 61.

was necessary to give this proof, which the author had not done. Biondi said that of all the researches hitherto made in connexion with the parasitic origin of malignant tumours, the only really important facts hitherto obtained, were the two positive results announced by Sanfelice ; and these undoubtedly gave food for thought.

Durante could not support the blastomycetic theory of the origin of malignant tumours, because the precise conditions which would enable him to say that the blastomycetes were really the causal factor were wanting. Sanfelice's experiments were lacking in this respect. He had seen his specimens ; but was not convinced as to the epithelial nature of the experimentally produced tumours.

Maffuci and Sirleo,[1] as the result of numerous inoculation experiments on various animals, and of many culture tentatives with human malignant tumours, sum up their conclusions as follows : (1) On *a priori* grounds, the infective origin of malignant tumours is probable. (2) The infective agent has not yet been determined, by either histological or experimental researches. (3) Investigations relating to the infective agents of tumours, should not be limited to one class of parasites. (4) Among the blastomycetes, some have pathogenic properties. (5) The lesions induced by blastomycetes, are quite different from such new growths as carcinoma and sarcoma. (6) Pathogenic blastomycetes may induce septicæmia, suppuration, and chronic inflammatory changes of granulomatous nature. (7) Blastomycetes found in human malignant tumours, when inoculated into animals, have hitherto producd only ordinary inflammatory pseudo-plasms. The authors deny that malignant epithelial tumours can be produced in dogs, by pure cultures of blastomycetes, as Sanfelice alleges. (8) In human cancerous and sarcomatous tumours blastomycetes cannot always be demonstrated, either histologically or by culture. (9) In ulcerating human malignant tumours, blastomycetes may be found. (10) The conditions under which this happens, and the distribution of the blastomycetes, are such as lead to the inference that the infection has been superadded. (11) While not denying the possibility that blastomycetes may cause malignant tumours, the authors maintain that this has not been proved experimentally. The tumour-like swellings produced in animals, by inoculation with pure cultures of blastomycetes, are inflammatory pseudo-plasms (granulomata), and never true malignant tumours.

Corselli and Frisco[2] isolated and obtained pure cultures of blasto mycetes, from a sarcomatous tumour of the mesenteric glands of man With these cultures they inoculated guinea-pigs, rabbits, and dogs ; and in several of the animals thus experimented on, they claim to have produced similar sarcomatous growths.

Even before the Italian pathologists took the matter up, several well-marked instances of blastomycetic infection in humanity had been reported.

[1] *Arch. ed atti. d. Soc. Ital. di Chir.*, Roma, 1897, vol. xi., p. lxvii. ; also *Cent. f. Path. u. path. Anat.*, 1895, Bd. iv., S. 305 ; Bd. vi., S. 438 ; also *Zeits. f. Hygiene u. Infectionskrankheiten*, 1898, Bd. xxvii., S. 438 ; and *Il Policlinco*, vol. v., May, 1895.

[2] *Cent. f. Bakt.*, etc., 1895, Bd. xviii., Heft 12 and 13.

Thus, Busse,[1] in 1894, published the case of a woman, aged thirty-one, with a suppurating pseudo-sarcomatous tumour of the tibia, of slow growth ; in which he found, in the primary as well as in the secondary swellings, numerous blastomycetes, as determined histologically and by experimental inoculation of animals therewith. Pure cultures of these were also made ; and when rabbits, dogs, rats etc., were inoculated with them, suppurative local swellings resulted. In white mice these inoculations caused death, and the fungi were demonstrated in the animals' blood. Intra-peritoneal inoculation of rats, resulted in the production of enormous tumours, which often generalized.

The patient above referred to, who presented other signs of general blastomycetic infection, died thus thirteen months after softening of the tibial tumour, in a state of extreme marasmus. Besides the tibial tumour, similar swellings had formed over the sixth left rib and over the right ulna. At the necropsy, there was general enlargement of the lymph-glands, besides softening nodules in the spleen, kidney and lung. Histologically examined, all of these lesions teemed with blastomycetes, of which cultures were made, which succeeded best on potato. Besides these microbes, the tumour-like swellings comprised numerous giant-cells, and much immature connective tissue, with pus-cells etc.

Kahane [2] also demonstrated and made pure cultures of blastomycetes, from cancers of the uterus etc. ; and, in some cases of this kind, he claims to have seen similar parasites in the blood.

Curtis [3] of Lille has recorded the history of a soldier, with a large, soft, pseudo-myxomatous tumour in the upper part of the thigh, which clinically resembled sarcoma. There was another similar tumour in the lumbar region. These tumours were situated in the subcutaneous tissue. When laid open, the groin tumour looked like myxo-sarcoma. Histologically examined, large parts of it were comprised almost entirely of masses of blastomycetes—extra- and intra-cellular—supported by a vascular connective-tissue network. The tumour substance had contagious properties ; for, a fragment of it implanted into a rabbit—in the course of ten days—gave rise to a tumour, the size of a small orange, which also teemed with yeast-like fungi. The organism grew rapidly on potato and gelatin, multiplying by gemmation ; and it is named by the author *Megalococcus myxoïdes.* The injection of pure cultures into white rats and mice, caused tumours—like those in the soldier—to form at the seat, of inoculation, with metastases in internal organs etc.

These experiments by Busse and Curtis, taken in conjunction with those by Sanfelice and his followers, show that for mankind and animals, certain yeasts may give rise to quasi-malignant pseudo-plasms.

Monsarrat [4] claims to have isolated an organism from cancer, grown in various media, and to have inoculated animals with pure cultures of it, causing in them endotheliomatous new growths, whence the parasites

[1] *Cent. f. Bakt.*, etc., 1894, Bd. xvi., S. 175 ; also *Arch. f. path. Anat.*, 1895, Bd. cxl., S. 23 ; and *ibid.*, 1896, Bd. cxliv., S. 360.

[2] *Cent. f. Bakt.*, 1894, Bd. xv., S. 629 ; and Bd. xviii., S. 616.

[3] *Ann. de l'Inst. Pasteur*, 1896, t. x., p. 448.

[4] Proceedings of the Royal Society, 1900, vol. lxvi., p. 58 ; also *Liverpool Med.-Chir. Journal,* 1900, vol. xx., p. 318 ; and Transactions of the Pathological Society, London, 1905, vol. lvi., p. 272.

were recovered. These bodies were identical with the blastomycetes described by Sanfelice. Cultures were difficult to obtain; for, of twenty-seven mammary cancers systematically examined, only one yielded a positive result. The organism grew but slowly on ordinary media. In six cases he examined the blood of patients with advanced cancer, but in all the results were negative. Monsarrat's cultures soon lost their virulence, and became inert. Attempts to sustain or increase their pathogenic properties, by successive passage through guinea-pigs and other animals, were unsuccessful. In his latest publication (1905), Monsarrat maintains that this organism is the specific cause of mammary cancer, and by injecting it into guinea-pigs and dogs, he claims to have caused cancerous tumours in them; but, a committee of the London Pathological Society having examined his specimens, found in them "nothing suggestive of carcinoma."

Leopold [1] found blastomycetes in non-ulcerated cancers from different parts of the body. Of twenty such tumours examined, he obtained cultures from four. His best material was derived from ovarian cancers. A special feature of his work is the prolonged study he made of particles of cancer substance in hanging drops of sterile bouillon, in a specially constructed thermostatic microscope. In these preparations, some of which were preserved for 200 days or more, blastomycetes were seen in various stages of development; and their multiplication by budding was studied. The organisms isolated from all of these four cancers, caused glucose to undergo alcoholic fermentation. In fixed preparations, double-contoured and budding organisms, as well as round bodies, were found; and there could be no doubt as to their being blastomycetes.

The following experiments on animals were made:—(1) A small piece of fresh human cancer was implanted into the abdomen of a rabbit, with aseptic precautions: on the death of the animal, four years and five months afterwards, there was found a suppurating tumour in the abdomen and epithelial overgrowths in the lung. (2) Fresh cancer substance implanted in the abdomen of a rat was followed by death, with the production of "adeno-sarcoma" in the right groin. (3) A pure culture from cancer of the human ovary, injected into the testis of a white rat, caused the formation of a sarcomatous tumour at the seat of inoculation and of multiple sarcomata (myeloid and round-celled) in the abdomen.

In the material injected, blastomycetes were present; similar organisms were found in the experimentally produced tumours, from which pure cultures were again secured.

A curious feature of these experiments was the production of sarcoma in animals, with organisms derived from human carcinomata.

Of fifteen human malignant tumours removed with the strictest aseptic precautions, and examined for blastomycetes, Carini [2] got only one successful culture. This, he thought, was probably a contamination product. He never succeeded in producing a malignant tumour, by the injection of pure cultures into animals. Histological examination of forty-four human tumours (mostly malignant), showed the presence of "Russell's bodies" in eighteen. Similar bodies were found in non-

[1] *Arch. f. Gynäkologie*, 1900, Bd. lxi., S. 77. [2] *Il Policlinico*, April 15, 1900.

malignant tumours, and even in normal structures, such as the prostate. He considered that the staining reactions of these bodies were not really characteristic of blastomycetes.

Petersen and Exner,[1] experimenting on animals with Sanfelice's *Saccharomyces neoformans* and other blastomycetes, found that the cultures produced large nodules at the seat of inoculation, with secondary formations in the kidney, spleen, lungs and lymph-glands. None of these formations presented the structure of human cancer or sarcoma—they were rather granulomata, comprising many giant-cells and masses of the parasites. From the histological examination of many specimens, they concluded that the endocytes of human malignant tumours are very rarely due to parasites.

Cultures of yeasts from malignant tumours so seldom occur, that the few successful results may be ascribed to accidental contamination. Those animal and human diseases that have been recognized with certainty, as due to yeast infection (cutaneous ulcers, inflammatory swellings, endometritis, abscesses etc.), have no resemblance whatever to cancer. The tumour-like lesions produced by yeast inoculations are granulomata, and not true tumours.

Wlaeff and Weinberg[2] repeated Sanfelice's inoculation experiments, but failed to produce any tumour having the least resemblance to cancer or sarcoma. As a rule, only granulomatous swellings resulted; but, in a few cases, pseud-adenomatous, cyst-like, and papilliferous, formations followed. Wlaeff was able to exalt the virulence of pathogenic blastomycetes, by repeated passage through animals. Cultures thus treated produced different results when inoculated into various animals; in some they caused septicæmia, in others local swellings and cysts, and in guinea-pigs a cutaneous lesion like lupus vulgaris. Weinberg found that the cysts produced by injection of feebly virulent cultures, contained numerous more or less degenerate blastomycetes, the cyst wall being of inflammatory origin. Wlaeff isolated blastomycetes from the juice of a sarcoma of the human uterus, and obtained pure cultures of them. He also demonstrated their presence histologically in the tumour.

In subsequent publications, Wlaeff[3] concluded that, since numerous investigators have isolated blastomycetes in pure cultures from malignant tumours, and have by inoculation with these produced infective growths in animals, these organisms are the causative agents of malignant disease. For various non-malignant tumours (adenoma, fibroma, cysts etc.), he advocates a similar ætiology.

He prepared a serum for inoculating animals against malignant disease, and found that in rats and monkeys, it conferred protection against growths caused by blastomycetes. Wlaeff subsequently used this serum, for the treatment of sixty cases of human malignant tumours; and came to the conclusion, that, when it was injected early, before lymph-gland dissemination had supervened, it had a curative effect.

[1] *Beiträge z. klin. Chir.*, 1899, Bd. xxv., S. 769.
[2] *Bull. et mém. de la Soc. Anat. de Paris*, t. lxxiv., 1899, pp. 706 and 842; also *ibid.*, t. lxxv., 1900, p. 147; also *C. R. Soc. de Biologie*, 1900, lii., p. 759.
[3] *La Presse Méd.*, 1901, p. 145; and *Rev. d'Obstét. et de Gyn.*, 1904, No. 8, p. 164; also *C. R. Soc. de Biologie*, 1900, lii., p. 1030; *ibid.*, 1901, liii., pp. 106 and 285.

The serum employed was obtained from the blood of asses and geese, that had previously undergone a series of inoculations with blastomycetic cultures.

Foulerton [1] has made inoculation experiments in animals with various pathogenic yeasts. In most cases these caused death in from a few days to a few weeks. In many instances granulomatous swellings formed at the site of inoculation; and from these the yeasts were again cultivated. He concludes that: "Considerably more evidence than is now available must be brought forward, before we can form any opinion as to whether Russell's fuchsin bodies etc., are merely parts of the cancer cells themselves, or whether they are of the nature of animal or vegetable parasites." It is not improbable that some tumours, now classed as sarcomata, may really be due to yeast infection; but, "as to the exact causation of carcinoma we are still absolutely ignorant."

Klein,[2] having discovered a pathogenic yeast in some ordinary country milk, found that when inoculated subcutaneously into guinea-pigs, it produced tumour-like swellings at the seat of inoculation. When the animals were killed some weeks later, the tumours were found to be crowded with yeast-cells. Other guinea-pigs were inoculated with the juice of these tumours and with sub-cultures, with the result that similar tumours again formed, and death sometimes resulted. In the latter cases, yeast-cells were found in the blood. This yeast seemed to belong to the same group as the blastomycetes of Sanfelice.

Gilchrist [3] has described a case of skin disease ("blastomycetic dermatitis") in man, in which the lesion teemed with blastomycetes, which were seen multiplying by budding. He considers that most of the so-called parasites, in certain skin affections, are merely products of nuclear and protoplasmic changes of epithelial cells, and not organisms. Since formations of this kind are found in simple skin diseases, as well as in cancers, they can have no specific causal relation to malignancy. Clinically the above case resembled "scrofuloderma."

Gilchrist and Stokes [4] have since reported another example of human blastomycetic infection. In this case the patient was a man, aged thirty-three, with a cutaneous disease like lupus vulgaris. It began eleven and one-half years previously, as a pustular pimple on the back of his left ear. Thence the morbid process spread slowly over the face, the older parts cicatrizing. A similar lesion formed, soon after the initial outbreak, on the back of his hand; but this healed, on treatment with caustic, about four years after its first appearance. Six months later a third lesion appeared on the scrotum, which spread for a year, and then healed spontaneously. Other lesions formed on the left thigh, back of the neck etc., and likewise healed spontaneously after some time. There was no enlargement of the adjacent lymph-glands, and the patient's health remained good. There was no history of tubercle or syphilis.

[1] *Journal of Pathology and Bacteriology*, May, 1899, p. 57; also *ibid.*, 1900, vol. vi., p. 154.
[2] Transactions of the Pathological Society, London, 1901, vol. lii., p. 270.
[3] Johns Hopkins Hospital Reports, 1896, vol. i., p. 269.
[4] *Journal of Experimental Medicine*, January, 1898, vol. iii.; also *Bull. Johns Hopkins Hospital*, July, 1896.

Sections of the cutaneous lesions, on microscopical examination, showed numerous budding blastomycetes, in association with which were many almost typical tubercles. The organisms were mostly extracellular, comparatively few being included in the giant-cells. Pure cultures were obtained from the lesion, which grew well on potato and beer-wort agar. The cultures showed both budding forms and mycelium, although the latter was not met with in the lesion. A horse, a sheep, dogs and guinea-pigs were successfully inoculated, nodules forming which resembled tumours, especially in the lungs. Since the parasite did not ferment sugar, and produced mycelium in cultures, it might belong to the blastomycetes or oïdia. The authors suggest that all quasi-tuberculous lesions of the skin should be examined for similar organisms, which can easily be done by soaking unstained sections in liquor potassæ, when the organisms may be recognized under the microscope as doubly contoured refractive bodies.

A considerable number of somewhat similar cases have since been recorded, in some of which the lesions were very like those of ulcerated cutaneous cancer.

Owens, Eisendrath, and Ready[1] have described an instance of this kind.

Hyde, Hektoen, and Bevan[2] have reported the case of a man, aged fifty-six, with a peculiar form of skin disease caused by blastomycetes. It began four years previously, as a raised red tubercle which gradually extended; until, when it had attained considerable size, it was removed by operation. A warty growth then appeared on his hand. A year later this was extirpated, and examined by Hektoen. Sections under the microscope showed blastomycetes; and, in cultures, mycelium appeared. Rats and mice subcutaneously inoculated died in a few days; and similar organisms were found in the lesions as in the inoculation sites. A striking feature of the histological sections was, the epidermoidal hyperplasia and its branching ingrowths. In the vicinity were numerous small aggregations of leucocytes and miliary abscesses, and in these localities giant-cells were plentiful.

The numerous publications on this subject, have been ably reviewed and summed up in Ricketts'[3] interesting monograph, to which the reader is referred for further details as to the cases etc. He noticed that, in several instances, the cutaneous lesions were "carcinomatoid" in their gross, and even to some extent in their minute structural features; while still more cases simulated skin tuberculosis. Histologically the lesions comprised hyperplasia of the deeper layers of the epidermis, with ingrowing processes of the same, and infiltration of all the constituents of the cutis by leucocytes, with minute abscesses in the corium etc. The microbes producing these lesions comprised three types—oïdium-like (torula), blastomycetoid (saccharomycetes or yeasts), and hyphomycetoid (mould fungi), most of the organisms appertaining to the first-named group.

In addition to these skin lesions, in several recorded cases, the malady

[1] "Pseudo-epithelioma with Blastomycetes," *Annals of Surgery*, 1899, vol. xxx., p. 545.
[2] *British Journal of Dermatology*, 1898, vol. ii., No. 129.
[3] *Journal of Medical Research*, February, 1902; and December, 1901, p. 377.

presented in mankind as a generalized infection, with fatal issue in a few. Cultures were obtained from the pus, and from the diseased tissues. Attempts to produce the typical lesions in mankind, by inoculation with cultures, have so far failed—most individuals being naturally immune; animal inoculation has also generally been unsuccessful, but in a few cases tumour-like nodules formed, and oftener abscesses.

Foulerton[1] has published the results of further study of this matter, comprising the bacteriological examination of several hundred human malignant tumours. In the course of this research, various types of microbes were cultivated from many of the tumours examined; but, in not a single specimen, was a yeast found. Hence, he regards the presence of yeasts in such cultures as the result of contamination *ab extra;* and, the cultures actually obtained, he considers as due to aërial contamination, terminal infection, or invasion from an ulcerated surface. His general conclusions are as follows:—A hypothetical cancer parasite does not in any way elucidate the pathology of cancer. So far as theoretical considerations go, the probabilities are against the theory of cancer being a parasitic disease. There is no evidence that any of the parasites which have been described as the cause of cancer, have any ætiological relation to the disease.

Nichols,[2] as the result of a thorough study of the subject, has independently arrived at very similar conclusions, which he formulates as follows:—

Certain blastomycetes can live and multiply in human and animal tissues, producing local lesions, and disseminating in distant parts, *i.e.*, they are pathogenic. These lesions are never really cancerous. Blastomycetic infection is rare in humanity. Blastomycetes, as a rule, cause marked tissue proliferation, with but little infiltration by leucocytes, *i.e.*, their toxic power is small. The morphology of the so-called "cancer bodies," is not identical with that of the blastomycetes. Blastomycetes are not constantly present in human malignant tumours. Even if blastomycetes do occur in human cancers, they are never found in such relation to the morbid formation, as to justify the belief that they are the cause of the disease. A general survey of the ascertained facts, reveals no evidence of any weight, that blastomycetes have anything to do with the causation of human cancers.

Since Koch formulated his celebrated postulates, for determining the ætiological relation of a parasite to a given morbid condition, an additional test has been established by the study of agglutinative reactions. In this connexion, Malvey[3] has shown that the serum of animals inoculated with yeasts, has the power of agglutinating those yeasts. Tested in this way, the "cancer yeasts" fail to give any indications suggestive of casual relationship to cancer; for, as Brauha[4] has proved, the serum of cancer patients when thus tested, does not give the agglutin reaction.

Skchiwan,[5] recognizing the existence of blastomycetes in animal

[1] *Practitioner*, 1902, vol. lxix., p. 213; and Middlesex Hospital Cancer Reports, 1902, vol. i.

[2] Second Report of the Cancer Committee of Harvard Medical School, 1902, p. 80.

[3] *Cent. f. Bakt.*, etc., 1901, Bd. xxix., S. 688.

[4] *Ibid.*, Bd. xxx., S. 945.

[5] *Ann. de l'Inst. Pasteur*, 1899, t. xiii., p. 771.

bodies, has proceeded to study their fate under these circumstances. Working with *Saccharomyces subcutaneus tumefaciens* of Curtis, and other yeasts, he concluded that the destruction of pathogenic as well as of non-pathogenic blastomycetes, is effected by the digestive powers of leucocytes, which take up the living organisms and destroy them (phagocytosis). Skchiwan claims to have seen yeasts multiply by budding within the phagocytes. He concludes that the destruction of yeasts within the body takes place, in accordance with the general laws of phagocytosis. The capsule, which sometimes forms round blastomycetes embedded in the tissues, he regards as a defensive arrangement by the organism against the further spread of the parasites.

In concluding this section on the blastomycetes and their supposed relation to tumour formation, attention ought to be called to De Backer's[1] work in this direction. De Backer approached the subject from a totally different standpoint to that adopted, by any of those to whose work I have previously referred. He thought that by the introduction of blastomycetes into the body, an artificial phagocytosis might be set up, by which any pathogenic microbes that were present would be destroyed. Assuming that cancer was a germ disease, he proposed to treat it and other germ diseases such as tuberculosis, diphtheria, typhoid fever etc., by the injection of pure cultures of yeasts.

It appears that the phagocytic properties of the saccharomycetes and some other organisms, were known to Bruhat and De Backer as far back as 1892. During microscopical examination of some wine that had gone wrong, Bruhat noticed that some of the cells of the ferment (*Saccharomyces pastorianus*) had included in them other cells, viz., those of *Bacillus aceti*. The two observers then instituted a series of experiments for the elucidation of this phenomenon. They found that young cells of most kinds of saccharomyces, were very energetic phagocytes for all kinds of bacteria, englobing and digesting them. From this it seemed to follow, if Metchnikoff's theory of immunity were correct, that organisms of this kind, injected into the blood of animals infected with pathogenic microbes, would greatly assist the leucocytes in their phagocytic work, provided that they could exist in the blood and tissues of their host, without producing ill-effects.

To test the practicability of this method, guinea-pigs and other animals were inoculated with the ordinary yeasts of commerce; but, the results were not encouraging, for owing to the presence of impurities the yeasts often proved pathogenic, causing abscesses etc. Pure cultures of *Saccharomyces cerevisiæ*, injected with aseptic precautions, were therefore substituted, and these proved innocuous. The animals were next injected with pure cultures, mixed with sterilized fermentable matter; and experiments were made, which showed that under these circumstances fermentative changes occurred within the body of the animals experimented upon, which were none the worse for it. Animals infected with bacterial diseases, were next treated in the same way. Guinea-pigs infected with tuberculosis and diphtheria, recovered under this treatment.

[1] "De la Cancérose et de son Traitement par les Ferments purs." Clermont (Oise); also "The Ferment Treatment of Cancer and Tuberculosis," H. Manders, London, 1898.

The plan was then tried on man. Bruhat, offering himself for experimentation, was injected in the flank. At the end of five hours a chill occurred, followed by sweating and symptoms of mild intoxication. At the end of three days the reaction had quite ceased, and no harm resulted. The infection caused leucocytosis. Phthisical patients were next inoculated, and it is claimed that, in early cases, the disease was nearly always arrested ; and most other cases improved, the main condition for success being that the cultures inoculated shall be absolutely pure.

In the treatment of malignant tumours De Backer claims, with this method, to have achieved astonishing results: of sixty cases there were eighteen cures, lasting over some years ; and, in many others, the progress of the disease was markedly retarded.

Here mention may be made of the fact demonstrated by Pasteur, more than a quarter of a century ago, that the saccharomycetes can obtain every requisite for their growth in the human body, except that their main food, sugar, can be obtained only in small quantities. This deficiency explains the slow growth of these organisms in normal animal bodies, as compared with their rapid growth in sugar-containing media.

To explain the curative effects of these injections in malignant tumours, De Backer makes use of this hint. He noticed that many of his guinea-pigs, which had lived together in full liberty, while subjected to a long course of pure yeast injections, got very fat and at the same time became sterile ; so that, even when occasionally impregnation did occur, the fœtus failed to develop. He conceived that this sterility was due to diminished production of glycogenous material in the uterus etc., consequent on yeast injections. It is known that localities specially prone to cancer, such as the uterus, breast, liver, stomach etc., are normally rich in glycogen ; and, as Brault and others have shown, all malignant tumours are also remarkably rich in this material, which is said to be absent from granulomatous inflammatory new formations. Moreover, we know that the blood of cancer patients is also unusually rich in sugar-forming substances.

With these points in view, De Backer concluded that blastomycetes artificially introduced into the body, by using up its glycogen for their own growth, might check the pathological increase of this substance ; and so starve the young cancer cells, by depriving them of their essential nutriment. Thus the whole tumour would shrink ; for, as Brault had shown, the rapidity of the increase of malignant tumours was directly proportional to the amount of glycogen they contained.

In this connexion, it is interesting to note, that of late many instances of the association of malignant tumours with diabetes have been reported (Kappler, Boas, Kreutzmann, Tuffier, and others) ; and, most of those who have specially studied this subject, maintain that the diabetic state favours the development of malignant disease.[1]

It may be said to be established, as the outcome of these and other experiments, that injections of yeast produce leucopenia, which is rapidly followed by leucocytosis ; with consequent large increase in the antiseptic substances, normally present in the blood-serum.

[1] For some further remarks on this subject, *vide* Chapter XVI.

### Mould-like Fungi.

Even as far back as 1879, I became aware of the fact that mould-like fungi grow readily in human tumours. This was particularly impressed on my memory by a case that came under my notice in that year, in the clinic of Broca, at the Necker Hospital in Paris.

The patient was a woman, aged fifty-eight, with a large, eroded, fungating, cauliflower-like tumour of the right breast. A lump had appeared in the breast, after her last confinement, nineteen years previously : eight years later, this heretofore comparatively stationary lump began to enlarge, the overlying skin ulcerated, and the tumour soon afterwards fungated ; the protruding mass was then cut off, but it soon grew again ; and the present tumour was the gradual outcome of this recrudescence. On examination this tumour was firm and non-adherent to the chest wall ; the nipple was not retracted ; and there was no enlargement of the adjacent lymph-glands. The diagnosis was fungating fibroma of the mamma. The breast with the tumour was removed. Histological examination showed that the real tumour growth consisted of fibro-cellular tissue, in which were embedded small cysts, lined by a single layer of cubical epithelium, evidently derived from the ducts of the mamma. The histological report, by Latteux, of which I still have a copy, says the appearances exclude the idea of sarcoma : " C'est, en somme, un fibrôme en voie de développement, tumeur essentiellement bénigne."

Now, the whole of the extensive surface of the fungating part of this tumour, was covered by a thick layer of coarsely mammillated granulation tissue ; which was pervaded throughout, to a considerable depth, by the mycelium and spores of a mould fungus,—of which Latteux's report gives a good sketch—although no trace of this parasite was noticeable to the naked eye.

The fungus was, of course, regarded as a mere epiphyte ; for, at that time, no one thought of ascribing the origin of tumours to such parasites.

In comparatively recent times, instances of spontaneously occurring granulomatous pseudo-plasms due to the mould-like fungi, have been met with in the skin (Schamberg, Ricketts, Delépine etc.), and in the gastric mucosa (Max Einhorn) ; and similar tumours have been artificially produced by injection of pure cultures of various mould-like organisms (Charrin and Le Play, Rothwell etc.).

An interesting case of this kind, which had been diagnosed after histological examination as " myeloid sarcoma," has lately been reported by Coley and Tracy.[1]

So far as I know, Bra [2] (" Le champignon parasite du cancer ") was one of the first to ascribe the causation of cancer, to the presence of organisms of this kind. By culture methods, he isolated from malignant epithelial and connective-tissue tumours, of various parts of the body, as well as from the blood of the patients, a specific cancer microbe, which he regards as an " ascomyces." His cultures were made by insemination of portions of the tumours, and by inoculations from the blood of affected

[1] *Journal of Medical Research*, 1907, vol. xvi., No. 2.
[2] *C. R. Acad. des Sci.*, Paris, 1900, t. cxxxi., p. 1012; also *La Presse Méd.*, 1899, vii., p. 87.

persons. The medium used was cow's udder bouillon, and the culture appeared as a scum and a sediment, after from five to eight days' incubation at 86° to 95° F.

The organism was of spheroidal or cylindrical form, and multiplied chiefly by sporulation, mycelia being formed. In dogs and rabbits, inoculated subcutaneously with these cultures, tumour-like swellings were produced, which histologically resembled malignant tumours—epitheliomata and sarcomata. By inoculating a bitch in the mammary region, Bra claims thus to have produced typical mammary carcinoma. From these artificially produced tumours, pure cultures were made, which contained organisms just like those found in the original tumour. The inoculations into guinea-pigs proved inert.

Curtis[1] of Lille, who repeated Bra's experiments, declares that after having taken precautions to eliminate extraneous organisms and other sources of error, neither cultures nor inoculation results could be obtained. He found that all tumours, even when not ulcerated and not contiguous to a free surface, nevertheless teemed with microbes; while ulcerated tumours simply swarmed with innumerable kinds of microbic life. He concludes that human cancers are neither cultivable nor inoculable; and that experiments hitherto published to the contrary, are due to errors of technique etc.

Niessen,[2] while examining the blood of a woman with advanced uterine cancer, found in it an organism, which he believed to be the cause of the disease. In this blood a dark green mould developed, which was cultivable. It proved to be an unknown species of organism, intermediate between a mycete and a mould. It grew with great luxuriance in human blood, in sterile diabetic urine, and in water; and the products of the cultures in these different media were themselves so diverse, that it was difficult to believe they were derived from the same source. This organism Niessen named *Canceromyces* or *Cladosporum cancerogenes*.

Braithwaite,[3] as the result of histological examination of sections of malignant tumours, found the morbid tissues pervaded by the spores and mycelia of a mould-like organism, which he regarded as the cause of the disease. Fungoid parasites were nearly always present in the specimens he examined; and he claims to have discriminated eight or nine different kinds of them in various forms of cancer, each corresponding to a particular variety of malignant disease. Braithwaite has also found fungoid organisms in non-malignant growths (*e.g.*, uterine myoma); hence, he conjectures that non-malignant tumours may also be of parasitic origin

### General Conclusions as to Blastomycetes etc.

Amid the hubbub of conflicting statements as to the relation of blastomycetes and malignant tumours, we may, I think, discriminate the following propositions:—

1. Certain blastomycetes are pathogenic for man and animals, and

[1] *Lancet*, 1899, vol. i., p. 801.
[2] *Cent. f. d. med. Wissenschaften*, Nr. 21, 1894.
[3] *Lancet*, June 29, 1895.

they may even cause in them lesions, which in their gross features somewhat resemble malignant disease. Thus, instances of pseudo-sarcomatous tumours, due to the presence of organisms of this kind, have been reported in mankind by Curtis, Busse, Coley etc.; while quasi-epitheliomatous lesions of similar origin, have been met with by Gilchrist, Owens, Hyde, Hektoen, and others. It also appears that certain oïdia (Obici, Ricketts), aspergilli (Rénon, Saxer, Boyce, Rothwell), bothryomycetes (Delore, Poncet), and probably other organisms, may originate similar morbid conditions.

That tumour-like swellings, which are often confounded with sarcomata, may be caused by actinomycetic infection, is now generally admitted by pathologists. Moreover, tumours of this kind are not particularly rare, and they have been seen in almost every part of the body. As Wolff and Israël have shown, pure cultures of these organisms, injected into rabbits, give rise to tumour-like swellings.

When carefully examined, these parasitic pseudo-plasms are found to differ markedly from true malignant tumours, both structurally and in their clinical features; and they should evidently be classed with the infective granulomata.

In consequence of these important discoveries, certain anomalous pseudo-malignant lesions, which have long puzzled pathologists and clinicians, may now be moved from the category of malignant neoplasms into that of the parasitic infections.

2. So many pathologists have succeeded in obtaining pure cultures of blastomycetes from human malignant tumours, that I regard the liability of the latter to blastomycetic infection as having been proved, although not a few investigators have failed to get positive results. Considering the richness of these tumours in sugar-forming materials, which are so favourable to the growth of blastomycetes, it would indeed be strange if they were not more prone to this kind of infection than the normal tissues of the body.

3. In their young and nascent condition, it has been repeatedly demonstrated, notwithstanding many assertions to the contrary, that non-ulcerated malignant tumours are quite free from blastomycetes.

4. The repeated failures to produce malignant tumours in animals, by inoculation experiments with cultures of blastomycetes, prove that the latter cannot be the specific causative factor of malignant disease. The few instances in which it is alleged that malignant tumours have been thus caused (Sanfelice, Bra, Leopold etc.), are capable of being otherwise explained (blastomycetic or other granulomata, spontaneously arising malignant disease etc.) The ensemble of many experiments clearly shows, that yeast organisms etc., are incapable of causing the formation of true malignant neoplasms (epithelioma and sarcoma).

### The Question of Infection.

In previous chapters,[1] I have already had occasion to refer to the subject of infection; but, to complete the matter, some aspects of this important question still remain to be studied.

[1] Chapters IV. and VIII.

In comparatively recent times, attempts have been made to utilize the irregularities invariably met with in the topographical distribution of cancer, as evidence of the infectious nature of the disease ; which, it is alleged, may manifest epidemic, endemic, and even pandemic characters. Hence, we now often hear of " cancer districts," " cancer houses," and even of " cancer rooms."

Arnaudet [1] was the first, who formulated ideas of this kind. In certain remote rural districts in Normandy, he found that cancer was twice or thrice as prevalent as in Paris, where the disease is of great frequency ; thus, in the little hamlet of St. Sylvestre de Cormeilles, the cancer mortality—for a period of eight years—averaged no less than 14·88 per cent. of the total deaths. He also adduced instances of cancers coexisting in various organs of persons living in certain houses or in their vicinity. Hence, he concluded that the locality where a cancer patient had lived was contaminated ; and he thought it probable that the contagion was spread chiefly through drinking polluted pond-water, which also contaminated the local cider, etc. Similar instances were soon afterwards advanced by Sorel, Guelliot, Fabre, Fiessinger, Webb, D'Arcy Power, Behla and others.

Webb [2] reported the following remarkable group of cases :

In a village not far from his residence were two houses under one roof, with water-supply and drainage in common. Let us call them Nos. 1 and 2. Twenty-six years ago a man aged twenty-eight, living in No. 1, died of cancer of the rectum. Mr. J. H. and his wife next occupied this house. His age was then sixty. Two years later he died of cancer of the stomach. His widow, who continued to live in the same house, died in it ten years later of cancer of the rectum.

Prior to her death, Mrs. R., aged fifty, who lived in No. 2, was found to have cancer of the breast, which ended fatally eight months later.

After the death of Mrs. J. H., No. 1 was occupied by three maiden ladies. Of these, Miss P. died four years ago, aged fifty-eight, of cancer of the uterus ; Miss F., who nursed her, died last winter, aged sixty-one, of cancer of the stomach ; the other sister was still alive and well.

None of these persons were blood relatives ; and, in none of the families, was there a history of cancer in other relatives.

In support of the infectious nature of the disease, it is alleged that the dwellers in certain houses, and even in certain rooms, may become affected with cancer, either simultaneously or successively, with undue frequency ; that instances of the disease attacking two persons living together (*cancer à deux*) are relatively frequent ; and that, in certain localities, so many cases may be met with as to constitute veritable epidemics.

Fiessinger [3] has met with several examples of such outbreaks.

Thus, in a small village, a woman died of cancer of the breast, and within a comparatively short space of time, two other women lodging in the house died of the same disease—one of the rectum and the other

[1] *Normandie Méd.*, 1890, iv., p. 33 ; also *L'Union Méd.*, Ap. 25, 1889 ; *Normandie Méd.*, Ap. 1 and Ap. 15, 1890 ; also Feb. 15, 1891. "Nouveaux faits à l'appui de la nature infectieux du cancer."

[2] *Birmingham Medical Review*, 1892, vol. xxxii., p. 342 ; also *ibid.*, 1894, vol. xxxvi., p. 209.

[3] *Revue de Méd.*, January, 1893.

of the vulva; and, after a certain time, two neighbours also died—one of cancer of the stomach, and the other of sarcoma of the leg.

He believes that these "epidemics" are particularly apt to occur on the banks of rivers, at the borders of woods etc., and he suggests that insects, which are plentiful in such places, are concerned in disseminating the disease, as well as contaminated fingers etc.

Guelliot [1] of Reims has reported forty cases, in which malignant disease appeared to have been spread by contagion. He claims to have proved: (1) that malignant disease is unequally distributed in adjoining districts, in such a manner that neither heredity nor consanguinity will account for it; (2) that there are real "cancer houses," the dwellers in which, in the absence of blood relationship, are nevertheless successively or simultaneously attacked by malignant tumours; (3) that cases of malignant disease attacking two persons living together are relatively frequent; and (4) that of one hundred such cases, eighty-five were man and wife, and eight were medical practitioners, who had been engaged in the treatment of cases of malignant disease. According to Guelliot, these facts show that cancer is an infectious disease, which is transmitted directly or indirectly by contagion. It is alleged that cancer is prone to occur in damp, low-lying situations, in the vicinity of sluggish streams, in marshy areas, in localities prone to floods, in sewage-saturated regions, in places having a retentive subsoil, such as clay, in the vicinity of trees etc.; and that this infection is spread by water, uncooked vegetables, insects, domestic animals etc.

D'Arcy Power [2] claims to have demonstrated localized epidemics of cancer in certain districts, villages, houses, and "even in a single room"; but, beyond the bald narration of certain exceptional occurrences, which of themselves are by no means convincing, he has not even attempted to prove his thesis.

Bosc,[3] having noticed the frequency of parasites and parasitic tumour-like swellings in fishes, believes that many outbreaks of cancerous disease are due to this cause. He thinks that gastro-intestinal cancer is often caused, by the bones of small fish wounding parts of the alimentary canal. External cancers, he maintains, are often due to infection carried by insects and various animals; by contaminated fingers and polluted water; and even by fleas, bugs, flies etc.

In a previous chapter,[4] I have referred to Haviland's interesting researches, as to the influence of local geological and topographical configuration in the incidence of cancer; and I have there explained my reasons for being unable to give them more than a certain limited acceptance.

In 1899, a committee appointed by the Birmingham Branch of the British Medical Association,[5] investigated the influence of locality on the incidence of malignant tumours, in parts of Warwickshire, Stafford-

[1] *Gaz. des Hôpitaux*, 1892, No. 139.
[2] *British Medical Journal*, 1894, vol. i., pp. 1240 and 1302; *ibid.*, April 27, 1895; also *Edinburgh Medical Journal*, 1902, vol. xii., p. 39.
[3] "Le Cancer," Paris, 1898.
[4] Chapter IV.
[5] *British Medical Journal*, 1899, vol. i., p. 812; also *Birmingham Medical Review*, May, June, and July, 1900.

shire, Shropshire and Worcestershire. They concluded, that there were districts in which this disease occurs with frequency much above the average, side by side with other districts in which it is rare. The high-mortality districts were usually poorly drained, flat, low-lying or bordering on streams ; whereas the low-mortality districts, were high, dry, and well drained. They believe that there is a direct connexion between the presence of subsoil water within a certain distance of the surface, and the prevalence of malignant disease.

They also found that second and third cases of cancer occur in particular houses, more frequently than can be accounted for by coincidence ; that particular groups of houses, perhaps in the same street, may be similarly affected ; and they suggest that this association implies contaminated soil. Old houses also appeared to furnish a higher proportion of cancer cases, than new ones.

Scott,[1] after having studied the prevalence of cancer in the Chelmsford and Maldon districts of Essex, concluded that whatever truth may underlie Haviland's theory, it is insufficient to explain the distribution of cancer in these parts. Essex is a flat, marshy county, with a clayey subsoil, and it used to be the home of malaria ; yet the cancer death-rate for the county is by no means high, being below the average for England as a whole. Although the unions of Chelmsford and Maldon, contain an excessive proportion of marshy land and estuary ("saltings") ; yet, their cancer death-rate, is less than that of the whole county. Those parts of the two unions which include the greatest extent of muddy foreshore, creek, and "saltings," have a smaller cancer mortality, than that of the whole of the two unions taken together. The disease was found not to be specially prevalent, in places situated on the banks of the fresh-water rivers. In these parts of Essex, therefore, the cancer mortality bears no evident relation to the variations in the physical features of the country.

Noël[2] finds that in "cancer districts" certain contagious, tumour-like growths are often seen on the trees, which have a certain resemblance to malignant tumours. He thinks that between these "arboreal cancers" and human malignant disease, there is some ætiological connexion, for the latter are of frequent occurrence in persons living surrounded by or near woods. Cancer of the lip, he says, never originates in Lyons ; but all those having the disease in that city, are found to have contracted it in the country. Noël considers it as proved that insects, especially certain wasps, have a special predilection for "arboreal cancers" ; and that they carry the infection not only from tree to tree, but also disseminate it (through orchards etc.) in human foods. He maintains that human beings may thus be infected ; when the contagion enters by the mouth, gastro-intestinal lesions result, while external parts are attacked through contact infection.

Behla[3] believes that cancer is a parasitic disease, which may be propagated like malaria ; and both maladies have, he thinks, some relation

[1] *British Medical Journal*, 1900, vol. ii., p. 420.

[2] "Sur la topographie et la contagion du cancer," *Rev. des Mal. Cancéreuses*, Paris, 1896-1897, ii., pp. 137 and 201 ; also *Thèse de Paris*, 1897.

[3] *Cent. f. Bakt.*, etc., 1898, Bd. xxiv., pp. 780, 829, 875, and 919 ; also *Zeits. f. Hygiene*, 1899, Bd. xxxii., p. 123, etc.

to damp, marshy conditions of soil. But differences in the soil, in the well-water, or in the atmospheric conditions, cannot account for such diversities in the incidence of the disease, as he has noted in different sections of the small agricultural town of Luckau ; thus, only the food remains. The inhabitants of the suburb in which cancer is so prevalent, are mainly small farmers and nursery-men, who eat large quantities of the uncooked vegetables, which they raise—cabbages, radishes, water-cress, lettuces etc. Behla then points out, that these plants are liable to tumour-like diseases of parasitic origin, such as that caused in cabbages by *Plasmodiophora brassicæ*. He has found drinking-water and vegetables teeming with these parasites, which he maintains are the infective agents of human cancer. The great frequency of gastro-intestinal cancer, points to the food as the chief means by which the contagion enters the body.

The domestic animals—such as dogs and cats—as well as the rats and mice of Luckau, are prone to cancerous tumours ; and, Behla thinks that these animals may also be a source of contagion, by which the malady is communicated to mankind. He also claims to have proved that cancer clings to certain streets, houses, or groups of buildings, irrespective of their size and age.

Behla has made special study of the house incidence of all cancer deaths in Luckau—which comprises a stationary population of 5,000—for a period of twenty-two and a half years. During this period, about 1 in 25 of the total deaths for the whole town were due to cancer, which is not a very high ratio.

The central part of Luckau, which is low-lying and surrounded by ditches, comprising 3,000 inhabitants, furnished 65 cancer deaths. Of its 415 houses, in 33 there had been a single cancer death ; in 10, two such deaths ; and in 4, three cancer deaths.

Its eastern suburb Kalau, which is also low-lying and marshy, being intersected by irrigation channels for market-gardening, comprising 1,000 inhabitants, furnished 73 cancer deaths, or 1 in 9 of its total mortality. Of its 127 houses, in 45 there had been a single cancer death ; in 9, two cancer deaths ; in 2, three such deaths ; and in 1, four deaths. The cancer mortality of this suburb was fourfold that of the central part of Luckau. Of the 40 houses, comprising its main street, only 5 were without at least one cancer death ; and 56 of the total 73 cancer deaths, occurred in the houses of this street.

In curious contrast with the foregoing, the high-lying and dry suburb of Sando, comprising 1,000 inhabitants, had not a single death from cancer during the whole twenty-two and a half years.

In estimating the value of these data it must be borne in mind, that no information is given as to the social condition, age and sex distribution of the contrasted populations, which alone might suffice to explain much of these diversities, judging by the experience gained as to the cancer mortality of such places as Hampstead, Clifton and Bath, to which I have previously referred ; moreover, the same reticence is manifest with regard to hospital accommodation, heredity, and the method of registration. It is not stated what proportion of those attacked with cancer, in each of the respective parts of the town, were treated and died elsewhere than at home. Then, again, it should be noted, that although the investigation comprised a series of years; yet, owing to the smallness of the community, the *massif* of the totals is far too small to enable reliable averages to be deduced therefrom. Hence, as evidence of infection, these much-paraded data have *per se*, but little scientific weight.

From study of the cancer incidence in the Nuneaton and Stratford-on-Avon districts, E. N. Nason [1] concludes, that cases of cancer tend to group themselves chiefly in the vicinity of sluggish streams, and where the subsoil is indifferently drained, sewage-polluted etc.

Lloyd Jones [2] has worked out the local distribution of malignant disease in Cambridge and its vicinity, during a period of nineteen years. He concluded as follows: (1) that some parts of the town are comparatively free from the disease, while other parts, often contiguous, suffer severely; (2) that elevated sites are less liable than low-lying ones; (3) that the chalk subsoil is the freest from the disease; (4) that proximity to the river is not always attended by a high cancer death-rate, although damp sites favour the disease; (5) that proximity to trees, especially large ones, in some way favours the prevalence of cancer; (6) that decaying vegetation, filth, collections of manure etc., are often found in cancer districts.

Mason [3] has in like manner examined the problem of cancer distribution, for the Leamington district of Warwickshire. He believes, whatever the ultimate cause of the disease may be, that it will be found to be associated with a sewage-contaminated subsoil; that end houses of rows, corner houses of streets, and houses on either side of court-entries are often "cancer houses," owing to drain leakages and consequent sewage contamination being most frequent at those spots; that old houses are more dangerous than modern ones for the same reason; and that houses built on porous subsoil (sandstone, gravel etc.), are more prone to favour the development of cancer than those built on clay.

Gifford Nash,[4] from the study of the distribution of cancer in North Bedfordshire, has arrived at the following conclusions:—

1. That the occurrence of cancer in that district, is a little above the average for England and Wales.

2. That cancer appears to be less common in the urban, than in the rural districts.

3. That the liability of the disease to attack the alimentary system is very great.

4. That the percentage of cases at an elevation of 300 feet, is considerably greater than under 150 feet; and also greater than that of the villages adjacent to the river Ouse. Hence proximity to the river, low elevation, liability to floods etc., does not increase the tendency to cancer.

5. That the nature of the soil appears to have very little influence on the occurrence of cancer.

[1] *British Medical Journal*, 1898, vol. i., p. 679.
[2] *Ibid.*, 1899, vol. i., p. 813. [3] *Ibid.*, 1902, vol. i., p. 139.
[4] "Cancer, with special reference to its distribution in North Bedfordshire," 1903.

6. That the large number of instances in which two or more cases occurred in the same house, or in persons intimately associated, points to the disease being infectious.

7. That infection, if it exists, is a very slow one, the usual interval between two cases in the same house and family, being about two years; and the liability to infection increases with age, very few cases occurring under forty years.

Symons[1] has made a careful inquiry as to the relation of cancer to the dwelling-house, as met with in Bath, a town of about 50,000 inhabitants, which has a high and progressive cancer mortality, with a low and diminishing tubercle death-rate. Its population, of whom two-thirds are females, has been stationary for the last half-century. This excess of females is largely due to the number of young women, employed as domestic servants etc. The population of Bath also comprises an unusually high proportion of middle-aged and elderly persons, especially females; and comparatively few children under five years old. Another of its peculiarities is the well-to-do-ism of its inhabitants, the proportion of persons of "independent means" residing there, exceeding that of any other town in England. Its general health and sanitary conditions are good, typhoid fever and infectious diseases are rare, its general and tuberculous death-rates are low, and in all these respects progressive improvement is noticeable; yet withal, its cancer mortality is very high, and for the last half-century it has been steadily increasing, until, at the present time, its corrected death-rate from this cause is 50 per cent. in excess of the average for the vicinity.

This city is situated in a deep valley—in the midst of hilly country—which is traversed by a sluggish, sewage-contaminated river, prone to flood the adjacent lands; it has a dense surface soil, overlying lias and oölite, which is permeated by numerous ground springs, the water being very hard. The town comprises many hills, and is surrounded and somewhat shut in by them; so that, although most of the houses lie in the hollow, many are built on the slopes of the hills, and most of the best residential houses enjoy quite elevated sites.

In order to get at the facts, as to the precise local distribution of malignant disease in the town, Symons located houses, 1,212 in number, in which 1,319 deaths from this cause had occurred during a period of thirty-two years (1866-1897), among 8,507 houses. Of the houses in which these deaths occurred, the great majority, viz., 1,111, had only a single fatality in each house; in 95 houses there had been 2 fatal cases; and there were 6 houses in which 3 cancer deaths had occurred. These numbers were so little in excess of those that the usual mathematical method of calculating probabilities indicated, that Symons concluded neither the elevation, nor the aspect, nor the class of house, had any constant relation to the incidence of the disease; and thus it was proved, so far as Bath is concerned, that there are no "cancer houses" there.

Applying this method to the data for Cambridge, as compiled by Lloyd Jones—who found that in nineteen years, among 5,685 houses, 438 had harboured persons who had died of cancer, of which only 7 houses

[1] *Public Health*, December, 1898.

had double cases and 3 triple ones—Symons showed that this proportion of multiple fatalities was actually less, than that indicated by the calculated probabilities; so that in Cambridge, as in Bath, there were shown to be no "cancer houses."

Hence Symons concludes, that there is no scientific basis for the doctrine of "cancer houses."

### General Conclusions as to Infection.

As I have previously indicated, no evidence in favour of infection is forthcoming from any of the large hospitals, in which numerous cancer patients are constantly under treatment; nor from those who are, in these institutions, constantly in close contact with their inmates.

It accords with this, that we never hear of "cancer epidemics" arising in the overcrowded parts of our great cities, where the density of population is at its maximum, and where sanitation is least regarded; but, it is rather from remote, sparsely populated, rural districts, that all the instances of this kind have come.

If cancer is an infectious disease, how is it that so few cases occur until after middle life; whereas, in other infectious diseases, it is the young who are specially predisposed?

It appears to me, for reasons I have previously set forth, that variations in the incidence of cancer mortality, can be far more satisfactorily explained, as the outcome of divergent conditions of existence, rather than as the result of infection.

Indeed, it is remarkable that a high local cancer mortality, nearly always coincides with and is indicative of, healthy surroundings; as is evidenced by the fact that there, the density of population is least, the tubercle mortality lowest, the average duration of life longest, the infantile and general mortality lowest, while infectious diseases are at a minimum: in short, among the wealthy and well-to-do, where the standard of health is at its best and life is easiest, there the cancer mortality is highest.

Of this in London, Hampstead is a striking example; in Bristol, Clifton; and in Bath, as we have seen, it is the same.

On the other hand, where sanitary conditions are least regarded, where the struggle for existence is hardest, the density of population greatest, and infectious diseases are most prevalent; that is to say, among the workers of our large towns, there the cancer mortality is lowest.

It accords with the foregoing, that malignant tumours are of great rarity in early life; and, at this period, the epithelial form of the malady is practically unknown: in all these respects malignant tumours differ from infectious maladies in general.

As against these weighty considerations, the curious medley of chaotic and conflicting statements, advanced by the advocates of infection in support of their thesis, seem to me to be of little worth. We need not seriously entertain these fairy tales, when their great progenitor—the hypothetical microbe of cancer—has been discovered.

## CHAPTER XI

# INFLAMMATION, TRAUMA, AND OTHER EXTRINSIC FACTORS

### Inflammation and Tumour Formation.

THE leading pathologists of the nineteenth century were more profoundly divided, as to the essential relations of inflammation and tumour formation, than on any other subject of the first importance in the whole range of pathology ; but, at the time, not much was said about it. These divergences, after having long lain comparatively dormant, have now under the stimulus of modern research flamed up again, in such a manner, that they cannot any longer be ignored.

In a previous chapter,[1] I had occasion to refer to the peculiar position taken up by Virchow in this matter ; how that he, so to speak, ran with the Broussaisian hare, and hunted with the Müllerian hounds, as if the processes of inflammation and growth were identical ; whereas, as I shall now proceed to show, they are in every respect fundamentally different and distinct. It is noticeable, moreover, that Virchow's neoplastic pathogeny [2] is throughout dominated by the Broussaisian conception, that tumours are but forms of inflammation ; whereas the Müllerian doctrine, that tumours are due to abnormal growth, is used merely as a subsidiary hypothesis, to make good the more obvious shortcomings and defects in the dominant hypothesis. It is Virchow's neoplastic pathogeny, thus vitiated *ab initio* by fundamental misconception, that the microbists have revived in recent times, accentuating its errors, with such results as I have set forth in the preceding chapter.

The leading British exponent of the Broussaisian doctrine of tumour formation is Jonathan Hutchinson,[3] who has formulated his views as follows : "The propositions in reference to cancer, which I am chiefly concerned to maintain, are : First, that it is a modification of chronic inflammation, and that the same laws which are applicable to the one are, for the most part, applicable to the other. Second, that it is under the influence of inherited tendency and of senility, that processes inflammatory in their outset tend to pass into those of cancer. Third, that cancerous processes are in their initiation local, and that the disease becomes constitutional by infection, by elements derived from the primary growth."

Among those who combated the fallacies of Virchow's tumour doctrine were Billroth and Cohnheim, both of whom, like J. Müller, rejected

[1] Chapter VII.
[2] *Die krankhaften Geschwülste*, Bd. i.
[3] *Archives of Surgery*, October, 1890, p. 138.

the inflammation theory. "A tumour," says Billroth,[1] "is a neoplasm that has not started from the same causes as excite inflammation; but from others that are unknown, or but vaguely suspected."

I think I have already made it sufficiently plain both in this and in other chapters, that my views on this important matter are entirely in accord with those of Müller, Billroth and Cohnheim; indeed, I believe that the Broussaisian doctrine of tumour formation, is mainly responsible for the comparatively small progress that has been made, during the last half-century, in tumour pathogeny—this misconception having given a wrong bent to the direction of tumour research.

For, since inflammation is the outcome solely of extrinsic causes, whereas the causes which determine tumour growth are mainly intrinsic, it is obvious that of these divergent and incompatible ways, only one can be right. In order to make this antithesis quite clear, it is necessary to state what is meant by this conventional term "inflammation"; which is used as a cloak for a complex of diverse processes, as to which there is to-day even less agreement among pathologists than formerly, when there never was unanimity.

The old conception of "inflammation," which summed up the mixed processes connoted by the term, as the aggregate of its cardinal symptoms —*rubor*, *dolor*, *calor*, and *tumor*, to which may be added *pyrexia*, is as true now as it was in the time of Celsus; because it is a mere description of externals, and does not concern itself with the underlying processes.

The most important of these processes undoubtedly is microbic infection *ab extra*; for, in the modern sense, there can be no inflammation without microbes. In accordance with this, we see that extensive injuries are repaired without inflammation when microbes are excluded, as in simple fractures; whereas, when this is not effected, the most violent inflammatory reaction ensues, as in compound fractures. Thus, the definition of inflammation, as "the succession of changes which occurs in a living tissue when it is injured," is altogether inadequate. The changes which take place in damaged structures, without the concurrence of microbes, by which *restitutio ad integrum* is effected, are an outcome of the reparative process; and have nothing to do with inflammation properly so called, although they are often improperly included within the scope of this term. Hence, we must also reject Grawitz' definition of inflammation, as "the reaction of irritated and damaged tissues which still retain their vitality."

"Inflammation" being the term originally applied to certain appearances met with in mankind, and thence extended to similar appearances in the higher animals, which are the outcome of changes concentring in the lymph-vascular system, it follows that inflammation in this sense, can only occur in organisms and tissues possessing such a system, and capable of reacting to foreign microbes in this particular way. In short, inflammation is, as Cohnheim says, a particular kind of disturbance of the circulation. Hence, non-vascular tissues, and organisms in which the lymph-vascular system is not evolved (as in the lower forms of animal life and in all vegetable organisms), are incapable of "inflammation."

[1] "Surgical Pathology," lecture xliv.

"No inflammation without bloodvessels," is quite as much a truism, as "no inflammation without microbes"; and, in both of these fundamentally important respects, there is complete antithesis between growth and inflammation—for the inception of growth is as independent of microbes, as it is of bloodvessels and nerves.

Lately the tendency has manifested itself, chiefly as the outcome of Metchnikoff's teaching, to identify "inflammation" with phagocytosis, and even with "chemiotaxis"; but this would be to substitute new names for an old process in defiance of historical tradition, which in the matter of names is the paramount authority.

Nothing has done more to obscure the fundamental antithesis between inflammation and tumour growth, than the failure of pathologists to discriminate between the phlogistic and the reparative processes, both of these perfectly distinct reactions being commonly included under the term "inflammation."

This is specially noticeable in the condition called "chronic inflammation," which in my opinion is not inflammation at all; but an abnormality of growth, the outcome of imperfectly co-ordinated reparative efforts. Hence, it would be well if the term "chronic inflammation" were altogether abolished from modern pathology, as being essentially misleading.

This confusion between "chronic inflammation" and the overgrowth marking imperfect repair, is the fundamental misconception which underlies and vitiates *ab initio* the Broussaisian doctrine of tumour formation, the fallaciousness of which I have now sufficiently laid bare.

## Precancerous Conditions.

It is an ancient belief, that cancer usually starts in a part of the body, which has undergone antecedent "inflammation," or some other departure from the normal; rather than in a part quite free from any such aberration.

As I have indicated in a previous chapter,[1] the proneness to originate cancer manifested by such pre-natal blemishes as "rests," moles, nævi, and other developmental irregularities, shows that there is such a thing as congenital local predisposition to the disease; and in this respect there is thus some warrant for the ancient belief.

Moreover, I am persuaded that well-ascertained facts indicate, that repeated irritations of long duration and moderate intensity are, in a certain proportion of cases, the precursors of malignant disease. Further, I am convinced that parts thus chronically irritated, may thereby be rendered more apt to take on neoplastic action, than they otherwise would have been. In short, there is such a thing as acquired local predisposition to cancer. Thus may we account for the relative frequency, with which certain cutaneous cancers are met with in chimney-sweeps, and other workers in irritant substances, such as tar, paraffin etc. Here also belong the various "eczema cancers," "lupus cancers," "scar cancers," "x-ray cancers" etc.

[1] Chapter VII.

The Broussaisians, however, are not satisfied to stop here; for, from such considerations as the foregoing, they draw the unwarrantable conclusion; that chronic inflammatory lesions are the necessary antecedents of cancer. It is against this doctrine that I protest; and I will now proceed to show its erroneousness.

The only evidence of any scientific value hitherto adduced in favour of the Broussaisian doctrine of cancer causation, is to be found in Volkmann's [1] well-known analysis of 223 cases of primary cutaneous cancer of the extremities. In this connexion, it must be borne in mind, that although the extremities suffer more from all kinds of traumata, scars, burns, chronic ulcers etc., than any other parts of the body, they nevertheless very seldom originate cancer. Of 7,297 consecutive primary cancers analysed by me, only 99, or 1·3 per cent., originated from the extremities; and of these, 72 started from the lower and 27 from the upper.

Now, Volkmann found that in no less than 88 per cent. of his cases, the cancerous disease had originated in connexion with some pre-existing lesion of the part; in only 12 per cent. did it appear to have sprung up spontaneously. If the state of things revealed by this analysis, were really representative of the ordinary mode of development of cancer, these data would be strong evidence in favour of the influence of irritation. But I maintain that it is not so. The cases analysed by Volkmann were not consecutive cases, but most of them had been recorded at various times by different observers, with the special object of showing the association between cancer and pre-existing local disease, as to the occasional occurrence of which there is no doubt.

The fallacy of accepting these data, as typical of what takes place in the ordinary development of cutaneous cancer, is well seen by comparing Volkmann's results with the following analysis of 40 consecutively occurring cases of primary cutaneous cancer recorded by myself,[2] in which special attention was directed to the question of pre-existing disease of the part. Of these 40 cases, only 11, or 27·5 per cent., were associated with pre-existing lesions—viz., old scars in 4 cases, congenital lesions in 2; suppurating sebaceous cyst, soot wart, wart of eighteen years' duration, recent wound, and chronic sinus, each in 1 case. In other words, the most careful examination, directed expressly to this end, failed to reveal the existence of any obvious pre-existing local disease, in 72 per cent. of all cases. In like manner, of 669 tumours analysed *ad hoc* by Rappok,[3] 32 per cent. started from some pre-existing lesion; and, in 68 per cent., nothing of the kind was noticeable.

By careful inquiries as to the association of the onset of cancer with pre-existing local disease, in other parts of the body, I have ascertained that, for these localities also, the foregoing conclusions are equally valid.

[1] *Samml. klin. Vorträge*, 1889, Nos. 334 and 335.
[2] Middlesex Hospital Surgical Reports, 1882 to 1889.
[3] *Deutsche Zeits. f. Chir.*, Bd. xxx., S. 465.

### In the Female Breast.

Thus, with regard to the *female breast*, it is often asserted that cancers of this part, are due to antecedent attacks of inflammation or abscess, yet no conclusive evidence of this has ever been adduced. Equally destitute of support is the constantly reiterated assertion, that the latter lesions are of more frequent occurrence in the cancerous, than in the non-cancerous.

The following facts are conclusive in this respect.

Winckel[1] has estimated that after 1,000 consecutive accouchements, mastitis developed in 6 per cent. This, of course, refers only to its frequency after single deliveries in a succession of women; and not to the frequency of its occurrence, in regard to the total pregnancies of each woman, during her entire puerperal life. To obtain the latter datum, Winckel's percentage must be multiplied by 4·6, this being the average number of accouchements of each married woman. Reckoned in this way, it will be found that 27·6 per cent. of all fertile married women have suffered, at some period or other of their puerperal life, from inflammatory disease of the breast. In order to ascertain what proportion of mammary-cancer patients suffer from similar affections, I made special inquiries on this subject in 137 cases. Of these, 24, or 17·5 per cent., gave a history of some previous disease of the breast—abscess in 15, sore nipple in 8, and inflammation in 1; and in 6 of these cases the nipples were congenitally malformed.

The above facts prove, that cancer patients are less prone to inflammatory diseases of the breast, than the non-cancerous.

Hence, the only basis for this alleged causation is, that in a certain proportion of cancer cases, inflammatory lesions have pre-existed. Moreover, against the assumed ætiological importance of previous inflammatory disease is the fact, that in most of the cases, the interval between the antecedent disease, and the subsequent outbreak of cancer, extended over many years; and, during this period, the breast appeared to be free from any lesion. Of like import is the fact, that cancer of the breast is relatively almost as frequent in the single and sterile as in the married, although the former are much less prone to inflammatory affections of the breast than the latter.

On *a priori* grounds, no inflammatory lesion seems more likely to be the precursor of cancer, than chronic mastitis; and; since this disease gives rise to circumscribed induration, its presence can hardly be overlooked.

Yet how rarely does mammary cancer ever appear to start in connexion with such indurations? I have met with this conjunction only twice, in 137 cases;[2] hence it seems to me improbable that chronic mastitis plays an important part in the genesis of mammary cancer.

[1] *Path. u. Therap. des Wochenb.*, 1878.

[2] According to Gross, cancer of the breast appeared to develop out of chronic inflammatory induration in 49 out of 907 cases, or in 5·4 per cent. (*International Journal of Medical Science*, March, 1888, p. 222).

### In the Uterus.

Similarly, with regard to *uterine* cancer, it is alleged by Emmet and his followers, that the disease is almost invariably caused by child-bearing, lacerations, "endometritis," or some of the other maladies incidental to the married state; while others attach great importance to catamenial derangements, the abuse of venereal pleasures, syphilis and gonorrhœa.

As I have previously mentioned, cancer is a disease of persons whose previous life has been healthy, and whose nutritive vigour seems to promise long life. It accords with this, that the natural functions of cancer patients are almost invariably performed with ease and regularity. Thus, in women with uterine cancer, the normality of the catamenial function is seldom disturbed; and, that it is established earlier and ceases later than in the generality of women, is an indication of vigorous sexual health.

Just so is it with regard to marriage, for a much greater proportion of uterine-cancer patients have been married, than of the female population of corresponding age.

Of 156 women with uterine cancer, under my observation, 146 (93·2 per cent.) had been married, and only 10 (6·8 per cent.) were single; similarly, of 168 cases tabulated by West and Duncan, only 3 were single; thus, of these 344 uterine-cancer patients, 311 had been married, or 96 per cent.; and only 13 were single, or 4 per cent. In the general population only 79 per cent. of women over 24 ever marry.

Of similar import is the great fertility of these cancer patients.

Of 143 uterine-cancer patients under my observation, only 6 were barren (4·2 per cent.); of 528 patients under treatment at the Berlin Charité Hospital (1883-1893) 28 were barren (5·3 per cent.): thus of these 671 patients 34 were barren, or 5 per cent. Among married women in the general community, the amount of sterility is much more than this; it has been estimated by Simpson at 11·6 per cent.

The 137 fruitful women in my list, averaged 5·6 children and 0·9 miscarriage each—the maximum progeny being 13 children and 4 miscarriages (of which there were 2 instances).

With regard to one-child sterility, there were 10 instances of it, or 1 in 13·7; which is almost identical with the ratio found by Ansell to prevail among fertile married women of the general population.

To sum up, 143 married uterine-cancer patients had between them 767 children and 123 miscarriages, the average being 5·3 children and 0·8 miscarriage each.

This amount of fertility exceeds that prevalent in the general community, which averages about 4·6 children and 1 miscarriage per marriage; when allowance has been made for the fact that a considerable proportion of uterine cancer patients die, before the completion of their reproductive life, it is obvious that their fecundity is even higher than from the foregoing figures it appears to be.

The mean age at first marriage (in 63 cases) was 21·6 years; and the mean age at which child-bearing commenced (in 100 cases) was 21·8 years; both of these averages are considerably earlier than the corresponding figures for married women of the general community; and they furnish another indication of the reproductive energy of these patients.

It will be gathered from what has been stated, that uterine cancer is of more frequent occurrence in the married, and in those who have borne children, than in the single and sterile. Must we infer from this, that frequent parturition favours the development of the disease? Certainly no such inference is warranted; for, as the following data show, female cancer patients in general, manifest a similar high degree of fertility.

Thus, 15 women with cancer of the rectum, averaged 6·3 children, and 0·7 miscarriage each; 98 breast-cancer patients averaged 3·4 children and 1·1 miscarriages each; 6 women with ovarian cancer, averaged 8·2 children each; 7 rodent-ulcer patients averaged 6·8 children and 2 miscarriages each; and 9 women with cancer of the tongue averaged 4 children and 1 miscarriage each.

It is evident, therefore, that the high degree of procreative capacity, manifested by these females, is merely one of the consequences of that exuberant general health and nutritive vigour; which, as I have previously mentioned, is a peculiarity of cancer patients.

It may be inferred, from the fact that 10 of the 156 uterine-cancer patients of my list, were unmarried, and all save one childless, that virginity is no safeguard against the disease; and, if this evidence as to virginity be deemed insufficient, reference may be made to many published cases in which the presence of uterine cancer has been demonstrated, in women who presented all the anatomical signs of virginity.

I have ascertained that in the great majority of uterine-cancer cases, the disease does not begin, until many years after the final cessation of child-bearing. Of 32 prolific women thus affected, interrogated by me, in 28 (87·5 per cent.) the disease did not begin until a year or more after the cessation of child-bearing, the average interval between the cessation of child-bearing and the onset of the disease, in these cases, being no less than 12·3 years.

Only rarely does cancer of the uterus arise during pregnancy (6 in 97 cases, or 6·2 per cent.); and within a year after parturition its occurrence is equally rare (6 in 97 cases).

These facts corroborate my contention, as to the independence of the outbreak of the disease, of the incidents of the reproductive life.

Here it must be mentioned, that the subjects of cancer of the corpus uteri are much less prolific, than those with cervical cancer.

Of 31 cases of this kind tabulated by Pichot, Ruge and Veit, 14 (45 per cent.) were absolutely sterile and 3 had only 1 miscarriage each; while the remaining 14 had between them 57 children: thus, of these 31 women, the average progeny was only 1·7 children each. When we recollect the comparatively late age at which this form of the disease supervenes, the significance of these figures is enhanced.

As I have previously pointed out, the ensemble of facts relating to the life-history of the subjects of uterine cancer shows, that they have almost invariably led regular, sober, and industrious lives. Persons of drunken and dissolute habits are comparatively seldom affected. Of 160 uterine-cancer patients consecutively under my observation, not a single one, so far as I could ascertain, had ever been addicted to prostitution; and, what is still more remarkable, only one presented undoubted signs of having had syphilis.

In this connexion, the almost complete immunity of uterine-cancer patients from chronic ulcer of the leg, is worth noting; among my cases there was not a single instance of it.

According to Glatter, of 365 Vienna uterine-cancer patients, 91 (nearly 25 per cent.) had been prostitutes; but, it must be remembered, that he arrived at this conclusion in a rather peculiar way—viz., by assuming that all those described in the registers as "Handarbeiterinnen," were—as a matter of course—"Lustdirne," which seems to be an unwarrantable assumption. At any rate, my experience in this respect is diametrically opposed to Glatter's conclusion; and in this I am in accord with Duchâtelet, Lebert, Walshe, Winckel, Tanner and Schroeder. The high fecundity of uterine-cancer patients strongly favours my views; for, a large proportion of prostitutes are sterile, or relatively infertile.

Martin, Bruns and others, think that previous attacks of gonorrhœa, predispose cancer of the uterus; but they have adduced no convincing arguments in support of this theory, which is at variance with all the information at my disposal.

With regard to the influence of *lacerations*—which may be associated with sub-involution, endometritis, hyperplasia, erosions, polypi etc.—in the causation of uterine cancer, some gynæcologists have gone so far as to assert, that the disease always or frequently originates in them.

In order to show the fallacy of this view, it is necessary to bear in mind the following facts about lacerations. They are usually confined to the inferior segment of the uterus; and at first labours they are of such frequent occurrence, as to be regarded by many gynæcologists as inevitable. Injuries of this kind are almost always multiple; and in the majority of cases the lesion is bilateral, being most marked on the left side, opposite the situation usually occupied by the fœtal occiput. In extent and depth they are variable, but in most cases the injury is only slight. The worst tears are met with after very rapid, tedious and instrumental labours. The occurrence of congenital cervical fissures, very like the traumatic ones, and in precisely similar situations, has been demonstrated by Fischel; and it is probable that the latter are often confused with congenital flaws of this kind.

Emmet and his followers regard lacerations as a veritable Pandora's box of uterine maladies; in fact, the number of diseases they ascribe to this source, wellnigh exhausts the list. With regard to cancer, they even go so far as to assert, that in all cases the disease originates in lacerations.

The only evidence adducible on behalf of these extreme views is the great frequency of lacerations; which, of itself, is of course quite insufficient, even when the two morbid conditions coexist. In cases of this kind, carefully observed by John Williams, in not a single instance did the cancerous disease appear to have started from the laceration.

Against any such theory it may further be objected; that if uterine cancer really originated in lacerations, it would—like the latter—nearly always be multiple, and its precise seats of origin would correspond with the localities in which lacerations usually occur; but, in the initial manifestation of the disease, none of these conditions are fulfilled.

Moreover, against the assumed ætiological importance of lacerations, is the fact; that the interval between the laceration and the outbreak of cancer, extends over many years, and during this long period the uterus appears to be free from disease.

Thus, the average age at which child-bearing commenced in my cases was 21·8 years; whereas in the same women the average age at which uterine cancer supervened was forty-four years: thus, between the outbreak of the disease and its alleged causation, a period of no less than 22·2 years intervened.

Of like significance, as previously mentioned, is the long interval usually found between the cessation of child-bearing and the onset of cancer.

Another indication pointing in the same direction, is furnished by the fact, that rapid, tedious and instrumental labours—after which lacerations are commonest and most severe—are relatively rare in uterine-cancer patients.

Of 65 cases in my list, in which the character of the labours was noted; in 59 they were natural (tedious or difficult in 9), and in only 6 were they instrumental.

Thus, notwithstanding many allegations to the contrary, no reliable evidence has hitherto been adduced, of any connexion between antecedent morbid affections of the uterus and cancer.

The great majority of the patients under my observation, had been remarkably free from previous uterine disease of any kind.

Of 137 cases in which special inquiries were made, only 13 had suffered from previous disease of the uterus; viz., leucorrhœa 7, prolapse 3, and endometritis 3.

This is in entire agreement with the facts previously mentioned, as to the good catamenial health of these patients, their remarkable fertility when married, and the ensemble of their life-history.

Since this was written, it has been pointed out to me that West[1] had previously come to the same conclusion; thus he says: "It may be supposed that we shall find indications of previous uterine disorder (as some suppose of uterine inflammation), out of which cancerous disease has been subsequently developed. Evidence, however, seems to be directly opposed to this supposition; for, in the history of only 5 out of the whole 170 uterine-cancer cases, is there any mention of previous uterine ailment."

The great rarity of cancer of the procident uterus is a fact of like import. Schmidt[2] reports that of 294 cases of cancer of the uterus under treatment at the Halle Clinic, only 2 were associated with pro-

[1] "Diseases of Women," 1864, p. 365. [2] *Monats. f. Geb. u. Gyn.*, Bd. vii., Heft. 5.

lapse; and of 423 women admitted for prolapse, only 2 were found to have cancer as well.

These facts were well known to the great Cruveilhier,[1] who pertinently remarks: " On doit s'étonner que le col utérin qui est si souvent le siége de dégénération cancéreuse, alors qu'il occupe sa situation normale, devienne si rarement malade dans le cas de prolapsus."

Of similar import is the great rarity of cancer arising from uterine polypoid pseudo-plasms, of which comparatively very few cases have been recorded.

### Gastric Ulcer and Gastric Cancer.

It is claimed by some practitioners, that most cases of gastric cancer originate from local ulceration. Thus, according to Mayo Robson,[2] " Every cancer, whether external or internal, follows on a pre-cancerous condition, such as cancer of the gall-bladder on ulceration produced by gall-stones, cancer of the stomach on chronic gastric ulcer, epithelioma of the penis on irritation under a phimosis etc." I propose to show that these conclusions are untenable, being completely at variance with well-ascertained facts.

Gastric cancer and gastric ulcer are such comparatively common diseases, that their not infrequent concomitance cannot be accepted as presumptive evidence of ætiological relationship.

The probability of any such causative connexion existing between the two maladies is contra-indicated, among other considerations, by their diversity in localization.

Thus, cancer of the stomach, so frequently originates at the pylorus, that it is commonly spoken of as pyloric cancer; analysis of 4,574 cases of gastric cancer (Brinton, Welch, Gurlt, Habershon, Luton and Fenwick), shows that in no less than 2,724 of these cases, or nearly 60 per cent., the disease was thus located. On the other hand, Welch's [3] analysis of 793 cases of gastric ulcer, shows that only 95—or 12 per cent.—were pyloric in situation.

According to these data then, the great majority of all pyloric cancers arise in a situation, where local ulcers are of great rarity; and, consequently, they must usually be quite independent of any such antecedent lesion.

Moreover, the commonest seat of gastric ulcer is the lesser curvature—where 288 (36·3 per cent.) of Welch's 793 cases were located—which is a rare situation for cancer, only 12·2 per cent. of Brinton and Welch's numerous cases, originating there.

In like manner, the duodenum is frequently the seat of ulceration, of similar nature to that met with in the stomach, indeed, both of these localities are not infrequently concomitantly affected; yet, cancer of the duodenum is one of the very rarest diseases: for of 7,297 primary malignant epithelial tumours tabulated by me, consecutively under treatment at several of the chief London hospitals, comprising 499 intestinal cancers, only 4 originated in the duodenum; similarly, of 1,148 intestinal

[1] *Anat. Path.*, liv., xvi. [2] *Lancet*, 1904, vol. ii., p. 1547.
[3] Pepper's " System of Medicine " (art. " Gastric Ulcer ").

cancers, Ewald found that only 19 originated in the duodenum, and other statistical data are to the same effect.[1]

Another item pointing in the same direction, is the diverse sex incidence of the two maladies ; thus, while cancer of the stomach is of much greater relative frequency in males than in females, the female liability to gastric ulcer is largely in excess of that of males.

In illustration of this, the following data are conclusive : the Registrar-General's Sixty-first Annual Report shows that 21·4 per cent. of the cancer mortality among males was due to gastric cancer, the corresponding figure for females being 13·2 per cent. ; with regard to gastric ulcer, of 177 consecutive cases tabulated by me[2]—as occurring among 32,505 male and 28,175 female in-patients in London hospitals—117 were females and 60 were males, showing that the liability of the former is more than double that of the latter ; and data collected by others are of similar import (Welch, Saundby, Bulstrode etc.). According to Saundby,[3] on the basis of clinical data, women are twenty times as prone to gastric ulcer as men ; and Bulstrode reports, that of 500 cases—admitted into the London hospital, 1897 to 1902—402 were women and only 98 men.

The age incidence of the two maladies is also very different, half of all gastric ulcers being met with between the ages of 20 and 30, and almost the whole of them being comprised between the years 18 to 38 ; whereas comparatively few gastric cancers are met with before 40, the average age at onset being 51 for males and 40·5 for females, most cases being comprised in the decennium 50 to 60.

Finally, it may be mentioned that the clinical symptoms associated with gastric cancer, are seldom indicative of antecedent ulceration ; for, cancer of the stomach runs a rapidly fatal course, the average duration of the symptoms seldom exceeding fifteen months.

The cumulative weight of these diverse indications against there being, as a rule, any ætiological connexion between gastric ulcer and gastric cancer, is so overwhelming, as to be practically conclusive; although of course, I do not mean to deny that cancer may exceptionally originate from gastric ulcer.

### Gall-stones and Cancer of the Gall-bladder.

The very frequent association of gall-stones, with that rare disease, cancer of the gall-bladder, has induced many practitioners to assume a causative relation of the former to the latter ; and, in reference to this presumption, Mayo Robson says : " The preventive treatment for cancer of the gall-bladder is obviously, removal of the source of irritation." This conclusion seems to me without scientific warrant. To give it even some air of probability, it would be necessary to show that cancer

[1] Of 42,000 necropsies at Vienna hospitals, comprising 3,583 cases of cancer, of which 443 were intestinal, only 7 originated in the duodenum (Schlesinger, *Wien. klin. Woch.*, 1898, Nr. 10, p. 245). Eighteen thousand necropsies at Guy's Hospital revealed only 10 cases of primary malignant disease of the duodenum—6 sarcoma, 4 epithelioma (Perry and Shaw, Guy's Hospital Reports, 1894, vol. l., p. 214).

[2] " Influence of Sex in Disease," London, 1885, p. 28.

[3] *British Medical Journal*, 1900, vol. i., p. 121.

of the gall-bladder is of fairly common occurrence ; whereas, in reality, it is one of the very rarest cancerous manifestations : thus of 7,297 [1] cancer patients, under treatment in large London hospitals, I found that only 11 had primary cancer of the gall-bladder ; Gurlt,[2] in Vienna hospitals, reported only 5 instances in 11,131 cancer patients ; and Reiche,[3] from the mortality statistics of Hamburg, 48 cases (9 males, and 39 females) in 12,484 cancer deaths.

Moreover, of 115 necropsies on persons with gall-stones, Mosher [4] found only 2 affected with cancer of the gall-bladder.

In the face of these facts, it is surprising to find such a conscientious author as Rolleston,[5] stating that primary cancer of the gall-bladder " is by no means a rare disease," without adducing any evidence in support thereof.

In like manner Robson says : " This disease is not nearly so uncommon as was formerly believed " ; but, in support of this pious opinion, not one jot or tittle of evidence is adduced.

The great rarity of primary cancer of the gall-bladder, is thus shown to be an indubitable and incontrovertible fact. On the other hand, gall-stones are of frequent occurrence in the general community, Kehr and others having found them in about 10 per cent. of all adults, as determined by post-mortem examination. It follows from these considerations, that gall-stones can very rarely be the cause of primary cancer of the gall-bladder, even if we suppose—which is most unlikely in view of Mosher's data—that every gall-bladder cancer is caused in this way.

As I have elsewhere pointed out,[6] cancerous patients in general are more prone to gall-stones, than are the non-cancerous of the same age and sex in the community at large ; and Colwell [7] has recently estimated that the cancerous are two and a half times as prone to gall-stones as the non-cancerous, irrespective of the seat of the primary growth.

I submit that the foregoing data only admit of one interpretation, viz., that cancer of the gall-bladder is seldom, if ever, caused by the gall-stones so often found associated with it.

In cases of this kind, we must rather look to antecedent morbid conditions of the cystic mucosa, as being the determining factor of these concretions.

It accords with this, that calculous concretions of the kidney and renal pelvis, which are of common occurrence, are hardly ever associated with malignant disease of these parts.

### Phimosis and Cancer of the Penis.

With regard to the alleged causative connexion between cancer of the penis and phimosis, it is to be remarked that phimosis is one of the commonest anomalies ; and a very large proportion of the male population is affected in this way, often to an extreme degree.

1 *Vide* Chapter XVIII.
2 *Arch. f. klin. Chir.*, Bd. xxv., S. 420.
3 *Deutsche med. Woch.*, 1900, Nos. 7 and 8.
4 *Johns Hopkins Hospital Bulletin*, 1901, p. 253.
5 " Diseases of the Liver," etc., 1905, pp. 620 and 627.
6 Chapter XVI.
7 *Middlesex Hospital Archives*, 1905, vol. v., p. 148.

If, therefore, as alleged, phimosis is a potent cause of cancer of the penis, this particular local variety of cancer should be very common.

But, the ascertained facts show that it is far otherwise ; thus, of 2,669 men with cancer, under treatment in the chief London hospitals, I found that only 106 had cancer of the penis ; and of 2,891 similar cases in Vienna hospitals, Gurlt found only 108 thus affected ; therefore, rather less than 4 per cent. of these male hospital patients were affected with this variety of cancer.

Englisch's statistics,[1] embracing a much larger number of cases—namely 12,607—show that less than 2 per cent. (1·81) of all cancers in men, affect the penis ; the Registrar-General's Reports show that the rarity of cancer of the penis is much greater, than even these hospital data indicate ; for, of 9,685 men who died of cancer during the year 1900, only 100 died of cancer of the penis, or about 1 per cent. ; Reiche's[2] Hamburg mortality data (1872-1898) show a still smaller proportion, viz., only 17 cases in 4,906 male cancer deaths, or 0·34 per cent. ; while the United States Census Report, for 1900, shows that this local variety of disease is even rarer in that country ; since only 0·18 per cent. of the male cancer deaths were due to cancer of the penis.

The United States negroes are said to be more universally and more severely affected with phimosis, than any other race ; yet, for the year 1900—although the cancer death-rate of male negroes amounted to 28·6 per 100,000 living—not a single death from cancer of the penis was recorded during the whole year. This great rarity of cancer of the penis in negroes is fully confirmed by Rodman's[3] experience in Philadelphia, by the Louisville statistics, and by other independent testimony.

Moreover, it is worth noting, that Jews are as little liable to cancer of the penis as non-Jews.

If phimosis were really a potent cause of cancer of the penis, how very different all this would be.

### "Paget's Disease" of the Nipple and Areola, and Cancer of the Breast.

Attention was first prominently directed to this subject by Paget's well-known essay on "Disease of the Mammary Areola preceding Cancer of the Mammary Gland," which was published in 1874.[4]

He reported cases in which initial lesions of this kind were, after various intervals, followed by the formation of cancer in the breast ; and the conclusion was drawn that this sequence "very often" happened. In this, there can be no doubt, Paget was mistaken. Indeed, he admitted that the areolar affection might often be cured, without any ill consequences ensuing ; and Velpeau had previously reported many instances of this kind. Paget adduced no statistical data in support of his dictum, as to the presumed frequency of the cancerous sequel, for none were then available.

[1] *Allgem. wiener med. Zeit.*, 1902, No. 16.
[2] *Deutsche med. Woch.*, 1900, Nos. 7 and 8.
[3] "International Text-Book of Surgery," 1900, vol. ii., p. 734.
[4] St. Bartholomew's Hospital Reports, vol. x., p. 87.

Since then, however, the subject has been numerically investigated on a large scale; and it has thereby been proved, that cancer of the breast follows "chronic eczema" of the nipple etc., in less than 1 per cent. of the total cases: thus of 5,440 mammary cancers tabulated by various authors,[1] in only 41 (0·75 per cent.) did the disease begin in this way. Surgeons may therefore disabuse their minds of the idea, that "Paget's disease" plays an important part in the pathogenesis of mammary cancer. Areolar affections of this kind, which are rare,[2] are only exceptionally followed by the outbreak of mammary cancer; consequently, the mamma should never be extirpated for lesions of this kind, unless signs of concomitant malignant disease are also present.

### "Lupous Cancer."

Lately a great deal of attention has been given to this rare manifestation, which has been cited as evidence of the belief, that "inflammation may slide into cancer." With regard to this suggestion we may at the outset remark, that although lupus and cancer are very common affections and fairly often concomitant, yet "lupous cancer" is certainly exceedingly rare; it would be far otherwise if lupus had any special proclivity to cancer. Besides this, although lupus is a disease which supervenes in early life, cancer does not originate from it, until the patient has attained the cancer age; the most therefore that can be legitimately claimed for lupus, as a factor in the causation of cancer, is that it imparts local tissue proclivity. Oftener than not, "lupous cancer" is merely a "scar cancer," the outcome of chronic lesions determined by cicatrization of the local disease, or of repeated injuries of the part by operative procedures. As is well known, in lupus and in the scars resulting from its erasion etc., histological appearances which are very "epithelioma-like," are usual, even in the absence of all cancerous manifestations. For further information relating to this subject, reference may be made to the publications of J. Hutchinson,[3] Bayha,[4] Steinhauser, Wild and others.

### Leucoplasia, Syphilis and Smoking, in Relation to Lingual and Buccal Cancer.

In many parts of the body, such as the oral cavity, the outbreak of cancer is fairly often preceded by obvious hyperplastic changes—leucoplasia—of the surface epithelia.

Of 78 cases of lingual and buccal cancer, examined *ad hoc* by me,[5] lesions of this kind pre-existed in 18; of 80 similar cases by Butlin,[6] in

[1] Bryant, Gross, Delbet, J. C. Warren, Bergmann, Shield, H. Morris, Campiche and Lazarus-Barlow.

[2] "Of 15,000 women examined at the gynæcological clinic, Chambers met with only two cases" (Transactions of the London Obstetrical Society, 1880, vol. xxii., p. 266).

[3] *Archives of Surgery*, October, 1890, p. 138.

[4] *Bruns' Beitr. z. klin. Chir.*, 1887.

[5] Middlesex Hospital Surgical Report, 1888, p. 107.

[6] "Diseases of the Tongue," 1885, p. 265.

16; and of 61 by H. Morris,[1] in 13: thus of these 219 cases, leucoplasia pre-existed in 47, or in about 22 per cent.

In the great majority of these cancer cases, there was no indication of any such antecedent lesion; hence, it may be concluded that although leucoplasia predisposes to cancer, it is by no means a necessary or even usual antecedent of this malady.

Leucoplasia, according to Schwimmer,[2] is a rare disease; for, of 5,000 persons examined as to its presence only 20 were affected. It is of much more frequent occurrence in men than in women; for, of Neisser's 547 cases only 24 were women.

Far too little is as yet known of the natural history of leucoplasia, to enable us to say in what proportion of cases it eventuates in cancer; but, in an able investigation into this matter by the veteran Fournier,[3] of 321 tabulated cases, 97 or 30 per cent., ended thus. Of course, many of these patients came under notice with the cancerous disease already developed; so that it is impossible to say, that this percentage really represents the natural outcome of leucoplasia, as many slight cases would probably never apply for treatment. Hence it may be inferred that leucoplasia only exceptionally ends in cancer.

It accords with this that leucoplasia is usually a very chronic affection; and many cases have been recorded of from 25 to 45 years' duration, without having undergone any cancerous change; of 12 instances of this kind in H. Morris' list, in 5 the duration of the disease had exceeded 10 years.

Leucoplasia originates at a much earlier age than lingual cancer, for the average age at onset of H. Morris' 12 leucoplasia patients, was about thirty-nine years; whereas, the average age for the onset of lingual cancer I have found to be about fifty-four years. This accords with Barker's[4] results; for, of 29 cases in which cancer followed leucoplasia, he found that the average interval was rather more than 14 years.

It is thus noticeable that, even in patients with leucoplasia, lingual cancer does not supervene until about the age-period fifty to sixty, at which it usually eventuates in persons free from leucoplasia.

According to Fournier, 80 per cent. of 324 leucoplasia patients had been infected with syphilis; while, in the other 20 per cent. syphilis could be excluded.

Of 88 cases of cancer of the tongue and mouth, in which I made special inquiries, there was evidence of previous syphilis in 31; and of H. Morris' 58 cases in 12: in the other cases syphilis could be excluded.

From these figures, it is evident that syphilis plays a more important part in the causation of leucoplasia, than it does in lingual cancer.

It is the same with tobacco-smoking, for this habit is far more conducive to leucoplasia—"smoker's patch"—than it is to cancer.

Thus, of 247 leucoplasia patients, Fournier found that 97 per cent. were smokers; 182 of these were syphilitic subjects, of whom 96 per cent.

[1] Transactions of the Medical Society, London, 1884, vol. vi.
[2] Transactions of the International Medical Congress, London, 1881, vol. iii., p. 171.
[3] *C. R. Internat. Méd. Cong.*, Paris, 1900.
[4] "Holmes' System of Surgery," 1883, vol. ii., p. 516.

were smokers; and of 65 non-syphilitic subjects, 98·4 per cent. were smokers.

Hence, though syphilis or smoking alone may cause leucoplasia, the combination of the two gives the greatest proclivity.

With regard to the relation of smoking to cancer of the tongue and mouth, special inquiries made by me show, that of 77 cancer patients, 12 had never smoked; of the others, 41 had been great smokers, and 24 moderate smokers, while 11 of the smokers had also chewed.

The women of Western Europe seldom smoke, but this does not give them exemption from cancer of the tongue and mouth, although they are very much less prone to it than men.

I have seen it stated that, but for syphilis and smoking, there would be no lingual and buccal cancer; such facts as the foregoing show the absurdity of this statement. Besides, tobacco smoking was unknown in Europe prior to the discovery of America, while cancer of the tongue and mouth was then an old-established and well-recognized disease; and, with regard to syphilis in its present form, most of those who have specially studied the subject believe, that it also came to us from America. In Finisterre, where women habitually smoke short pipes, Hertaux never saw a single case of oral cancer, although the disease is common among men; and testimony to the like effect comes from other countries, where women have long been in the habit of smoking.

Special inquiries made by me, as to the precise situation of the initial outbreak of lingual cancer, show that in nearly half (48 per cent.) of the total cases, the edge of the tongue is the part affected; on the other hand, this is a comparatively rare site for leucoplasia, which in the great majority of cases affects the dorsum—a situation in which lingual cancer very rarely originates—only in about 5 per cent. of the total cases, according to my researches.

Again, a common site for leucoplasia is the angle of the mouth; but it is very rare for cancer to develop in this situation.

From these facts it may be inferred that, even when leucoplasia and cancer coexist, the latter disease often originates elsewhere than in the leucoplasia patch. A case reported by H. Morris [1] strikingly illustrates this feature; his patient had suffered from the papillary form of leucoplasia, affecting the dorsum of the tongue, for several years, when epithelial cancer of the lower lip supervened. Moreover, leucoplasia has been known to develop, after the outbreak of cancer, as in cases reported by Shield and Butlin.

From the consideration of the various items above set forth it may be inferred, that intrinsic causes are much more important factors in the origination of cancer than extrinsic ones; which are by no means its necessary antecedents. In the vast majority of cases, the outbreak of this disease appears to be entirely spontaneous; that is to say, it cannot be attributed to the immediate action of any appreciable extrinsic cause whatever.

[1] Transactions of the Medical Society, London, 1884, vol. vi. (Case 14 in Table III.).

## Trauma and Cancer.

Those who maintain that cancer is commonly caused by trauma must explain how it is that men, who suffer three times as often from traumata as women, are, nevertheless, only about half as liable to cancer.

Thus, of 9,229 consecutive cases of trauma under treatment at four large London hospitals, I have found that 6,856 were males and 2,372 females, or 2·89 males to 1 female. Similarly, of 240,063 deaths from traumata, tabulated by the Registrar-General for the twenty-five years 1848-1872, 178,005 were males and 62,058 females, or 2·8 males to 1 female. On the other hand, of 7,878 consecutive cases of cancer under treatment at the above-mentioned hospitals, 2,861 were males, and 5,017 females, or 1 male to 1·7 females. Similarly, of the 19,433 cancer deaths in England and Wales during 1890, 7,137 were males and 12,296 females, or 1 male to 1·7 females.

Evidently either these facts must be refuted, or the theory of the traumatic causation of cancer must be given up.

Still more cogent is reasoning of this kind when applied to cancer of the breast ; for, whereas men are quite three times as liable to traumata of this part as women, yet they suffer from mammary cancer only in the proportion of 16 to 1,863, or 1 male to 116 females.

Moreover, were mammary cancers thus caused, the nipple and areola would be more frequently affected than other parts of the breast ; but, as we have already seen, the actual proportion of cancers that arise from this part is less than 1 per cent., while the skin of the mammary region is even much less liable.

This completely negatives the alleged causation of mammary cancer by pressure of the corset, injury of the nipple in suckling etc.

Again, if the traumatic theory of cancer causation were true, those parts of the body most subject to injuries, such as the upper and lower extremities, the scalp etc., would be the commonest seats of the disease ; but its actual localization is totally different.

The great rarity of malignant epithelial tumours of the extremities and scalp, has much significance in this connexion : thus, of my 7,297 cancer cases, only 99 originated in the extremities (71 in the lower and 28 in the upper) ; while there were only 10 scalp cases. Moreover, of all parts of the hand, the palm, which is most exposed to traumata, is least liable to cancer.

Another item is, that the initial lesion of cancer is almost invariably solitary ; whereas, if the disease were of traumatic origin, it would often be multiple.

It is a curious circumstance, that advocates of the traumatic theory of cancer causation should have overlooked these obvious facts.

They base their belief in it on statements made by patients themselves, as to the antecedent occurrence of trauma. Of 137 women with mammary cancer interrogated by me, 35 gave a history of antecedent trauma, or 25·5 per cent. ; inot her words, the most careful investigation directed expressly to this point, failed to elicit any previous history of trauma in 74·5 per cent. of all cases.

In not a single instance was there any evidence that the disease had developed out of induration, or other obvious lesion thus induced.

In the cases under my observation, it seemed to me that injury was often merely the means of directing the patient's attention to the previously existing disease, of which she had until then been unconscious.

Of 1,000 cases of cancer consecutively under my observation, there was but a single instance in which the disease immediately followed an injury, and this was a case of so-called acute traumatic malignancy. Yet, if traumata were the efficient causes of cancer, such occurrences would be quite common instead of being so infinitely rare.

Moreover, we cannot produce cancer by any kind of traumatism, even in those who are already subject to the disease ; and their wounds heal just as do those of the non-cancerous.

The attempts made by Gilbert and Roger [1] to produce cancer of the mammæ of old bitches, by subjecting them to various forms of mechanical irritation, completely failed to attain this end ; and Cazin, by rubbing soot into the irritated parts, was equally unsuccessful, although the soot was taken up by the local cells, as we know is also the case in "chimney-sweep's cancer."

Though a blow, wound, or other injury may sometimes precipitate the formation of a cancer ; yet, it appears to me from the foregoing considerations, that such stimuli are of themselves inadequate to cause the disease. I regard the relation of trauma to cancer—to borrow a Darwinian simile—as resembling that of a spark in contact with combustible matter, the result depending upon the nature of the latter rather than upon the spark itself.

### "Traumatic Malignancy."

Among the clinical records of the last half-century, some rare instances may be found, in which the outbreak of malignant disease has appeared rapidly to follow severe local trauma ("acute traumatic malignancy"), as in cases reported by Barwell,[2] H. Cripps, Puzey and others. Careful study of the records of these rare cases—all of which are sarcomata—inclines me to admit the reality of this exceptional method of causation ; although, in some cases of this kind, the malignant growth undoubtedly antedated the alleged causative injury, as was the condition in the only example that has come under my own immediate notice.

Another group of cases, nearly akin to the above, comprises sarcomata developing at the seat of recent fractures, of which examples have been recorded by Shattock,[3] Griffiths,[4] Senn,[5] Haberen,[6] Pollard,[7] Virchow,[8] and others. In some cases of this kind—of which I have elsewhere reported an example [9]—the tumour preceded and was the cause of the

[1] *La Presse Méd. de Paris*, July 14, 1894.
[2] *British Medical Journal*, 1882, vol. i., p. 187, *et seq.*
[3] Transactions of the Pathological Society, London, 1896, vol. xlvii., p. 261.
[4] *British Medical Journal*, 1884, vol. i., p. 1125.
[5] "Pathology and Surgical Treatment of Tumours," 1900, p. 85.
[6] *Arch. f. klin. Chir.*, Bd. xliii., S. 352.
[7] Transactions of the Pathological Society, London, 1885, vol. xxxvi., p. 388.
[8] "Path. des Tumeurs," 1867, t. i., p. 482.
[9] Middlesex Hospital Surgical Report for the Year 1888, p. 269, No. 4.

fracture, rather than *vice versâ*. In other cases, however, the disease probably started from tumour germs, entangled in the reparative new formation, and incited thereby to abnormal growth ("callus-sarcomata" etc.).

From the fact that cartilaginous structures commonly abound in these tumours, it may be inferred that heterotopic elements of this kind are the germs whence most of them arise; and it accords with this, that some of these tumours are of an osteo-chondromatous, rather than of a sarcomatous, nature.

In like manner, hydatid and tuberculous diseases, sometimes develop in the callus of fractures.

Even many years after the original injury, malignant tumours have been known to originate thus.

In other parts of the body similar conditions are very exceptionally met with; *e.g.*, cancer originating in Röntgen-ray burn (C. W. Allen, Foulerton etc.), in an issue wound (Billroth), in an empyema wound (Young), in the wound after the operation of ventro-fixation of the uterus (Malone), in the scar of stumps after amputation, in old scars (especially of burns), in chronic sinuses etc.

In like manner, after the surgical ablation of non-malignant tumours, in very rare and exceptional cases, malignant disease may spring up in the wound: *e.g.*, after removal of mammary fibro-adenoma (Erichsen), of simple dermoid cyst (Wolf), of "desmoid" of the abdominal wall (Asken), of angioma (Pirogoff), of uterine myoma etc.

It is only after operations in which one or both ovaries have been removed, that occurrences of this kind are at all frequent; and this type of case, ætiologically regarded, belongs to quite a different category, as I shall subsequently have occasion to show.

I have also seen instances of the acute outbreak of malignant disease, after the surgical removal of fairly chronic cancers of the breast, uterus, cheek etc., in which it seemed likely that the acute post-operative exacerbation of the malady, might be ascribed to dissemination in the wound of particles of the disease, detached during the course of the operation, which had thus acquired increased capacity for malignant growth.

Perhaps the most remarkable feature about such cases as are comprised in this section, is their great rarity; to account for this, I can only surmise that the final outbreak is but the explosion of a long train of antecedent preparation; hence also the failure of attempts to reproduce similar results experimentally in animals.

## CHAPTER XII

## THE QUESTION OF THE ORIGIN OF MALIGNANT FROM NON-MALIGNANT TUMOURS

IMPORTANT practical issues are involved in the solution of this question, as to the alleged proclivity of non-malignant tumours to become malignant. If any such tendency really exist, then non-malignant tumours ought to be promptly extirpated.

Prior to the application of the microscope to the study of new growths, it was generally believed that every chronic tumour ("*scirrhous*") either was malignant or tended to become so. This dictum was long ago stigmatized by Lebert[1]—who showed its erroneousness—as: "A very convenient doctrine for surgeons"; and, as I shall proceed to show, this criticism still holds good.

The difficulty of then discriminating between malignant and non-malignant tumour-like swellings, rendered some such belief inevitable; but, since the utilization of the microscope for this purpose, it is surprising to find the old creed still so influential.

We now have to inquire whether, in the light of modern research, this belief is justifiable.

Since innocent tumours may inflame, suppurate, ulcerate, necrose, and degenerate, just like physiological parts of the body, it seems not unreasonable to suppose, on *a priori* grounds, that they may also become the seats of malignant disease. The occasional coexistence in the same organ, of benign and malignant tumours, favours this view. Such are the chief considerations which have given rise to the common belief, that innocent tumours are peculiarly apt to become malignant.

On critical examination of the subject, two considerations have much impressed me.

The first is the rarity with which these two kinds of neoplasms coexist in the same organ; so that, even if we admit that malignant transformation takes place in all such associated neoplasms, the event must be one of great rarity—very much rarer than it would be, if non-malignant tumours were especially prone to become malignant.

The second consideration is the inconclusiveness of the evidence, as to the malignant growths in most of these cases, having sprung from their non-malignant associates. In many instances, it is perfectly evident, that the association is a mere coincidence, each neoplasm having originated independently. In other cases, the coexisting neoplasms are more closely

[1] "Traité des Maladies Cancéreuses," Paris, 1851, p. 59.

associated; but, even in these, the appearance of the non-malignant tumours is often such, as hardly to countenance the belief that the malignant disease had sprung from them.

In short, a thorough examination of the subject in all its bearings has convinced me, that non-malignant tumours have no special proclivity to malignancy.

In support of this thesis, I now propose to discuss the evidence in detail, as it affects some of the more important organs.

### Uterine Myoma and Malignant Disease.

It must be borne in mind that uterine myomata are of very frequent occurrence, according to Bayle, 20 per cent. of all women over thirty-five are thus affected; and there are good reasons for believing, that the liability to these tumours increases still more with advancing years.[1]

If this estimate be correct—and so far as I can judge it is not very wide of the mark—these neoplasms are much commoner even than cancer (malignant epithelial neoplasm). Hence, considering the great frequency of both diseases in women of a certain age, we need not be surprised to find them coexisting in the same uterus rather frequently. Thus, of 78 uterine-cancer necropsies of my list, in 5 there were concomitant myomata; and of the 45 similar necropsies tabulated by Lebert, 6 were associated with myomata; thus, in these 123 uterine-cancer necropsies, myomata co-existed in 11, or in 9 per cent.

In estimating the significance of this concomitancy, the following items demand special attention.

1. In the immense majority of cases—in four-fifths of those under my own observation—the two neoplasms were quite separate and independent of one another—the myoma having sprung from the corpus and the cancer from the cervix or portio—so that, in these cases, there could be no question of the latter disease having originated from the former.

2. In the remaining cases, the coexisting neoplasms were more closely associated, most of them arising in the corpus. A common condition is to find one or more small subperitoneal or intra-mural myomata, with cancer of the mucosa. Under these circumstances, the fibroid is seldom cancerous. Of course, when the cancerous disease spreads widely, even fibroids such as these may be at length invaded.

3. A good many instances have been recorded of myomata projecting into the uterine cavity, and bearing on their surface a cancerous growth or ulcer. In cases of this kind, the cancerous disease usually spreads from the mucosa to the fibroid, by the way of the perivascular lymphatics. In like manner, uterine fibroids projecting into the abdomen, sometimes become cancerous through extension of the disease from adherent neighbouring organs, such as the ovary, intestine, and omentum.

4. There is yet another way in which fibroids may possibly be secondarily invaded by cancer, and that is by dissemination from a primary focus elsewhere, of which Schaper[2] has reported an instance, the primary

[1] *Vide* the author's book on "Uterine Tumours," 1901, p. 123.
[2] *Arch. f. path. Anat.*, 1892, Bd. cxxix., S. 61.

disease being in the lung, and Bender[1] a similar case, secondary to primary cancer of the mamma.

5. In such cases as the foregoing there is, of course, no question of the cancerous disease having primarily originated in the myoma. Indeed, this is an event of such rarity, that the great Cruveilhier, with his large and carefully recorded experience, never saw a single instance of it: hence he wrote:[2] " Les corps fibreux ne sont pas susceptibles de dégénération cancéreuse. Il y a incompatibilité absolue entre les corps fibreux et le cancer." Although we now know, that there is no such absolute incompatibility between uterine myoma and cancer, as Cruveilhier believed; yet, the extraordinary rarity of this morbid conjunction, is a noteworthy and well-determined fact. Thus, notwithstanding the great activity of modern pathologists, only about two dozen instances of it have hitherto been recorded;[3] and, in many of these, the evidence adduced as to the cancer having originated in this particular way, is far from being really convincing.

The frequent presence of epithelial structures in uterine myomata, as first demonstrated by Babès and Diesterweg, and confirmed by Ricker, Orloff, Recklinghausen, Landau etc., enables us to understand the source whence the cancerous disease of uterine fibroids originates.

Cases of this kind have been described by Klob, Coe, Rœhrig, Liebmann, Legueu and Marien, Rolly[4] etc.

Klob,[5] in describing the first case of this kind, says: " In 1862, a singular specimen was added to the Salzburg Museum. From the interior of a fibroid, the size of a child's head, situated in the posterior wall of the uterus, carcinoma had undoubtedly developed, without any other portion of the uterus being affected; and, I am therefore constrained to admit the possibility of such a transition; although I cannot recall a second case of this kind, either in the literature of the subject, or in my rather extensive experience."

In a case under my own observation, there was a large, encapsuled, fibroid tumour, the size and shape of a lemon, in the substance of the lower part of the posterior wall of the uterus, where it had compressed the rectum, and caused symptoms of intestinal obstruction. This tumour was infiltrated throughout by colloid cancer of the tubular type,which had also slightly invaded some of the adjacent structures. Several adjacent lymph-glands were invaded, but there were no metastases. The patient was a woman, aged forty-three, who had complained of difficulty in defæcation for the last twenty-five years.

Noble,[6] having analysed 1,188 promiscuously-gathered myoma cases, found that 29 of them were complicated by cancer of the corpus and only 12 by cancer of the cervix; this ratio being so much at variance with the usual standard of uterine-cancer localization, he concluded that myomata predisposed to cancer of the corpus. If his cases were really represen-

[1] *Bull. et Mém. Soc. Anat.*, Paris, October, 1904.
[2] " Traité d'Anat. Path. Gén.," etc., liv. iii., p. 661.
[3] Piquand, " Les Dégénérescences des Fibro-myomes de l'Uterus," Paris, 1905. etc.
[4] *Anat. f. path. Anat.*, 1897, Bd. cl., S. 555.
[5] " Path. d. weibl. Geschlechtsorgane," 1864, S. 163.
[6] *American Medicine*, September 10, 1904.

tative, such a conclusion would be legitimate ; but we know that cancer of the cervix is an easily diagnosed disease, and it is not likely that many patients thus affected would be sent to the surgeon to be operated on for myoma. This is undoubtedly the explanation of the paucity of cases of cancer of the cervix comprised in his list ; hence his conclusion must be rejected, as being essentially misleading.

If such conditions were of common occurrence, cancer of the uterus would be more frequently met with in the *corpus* than elsewhere, for it is here that over 90 per cent. of all uterine myomata originate ; but we know that only about 5 per cent. of uterine cancers arise from the *corpus*.

It follows from what has been stated that, far from uterine fibroids having any special proclivity to become cancerous, they are very much less prone to originate this disease than are the epithelial elements of the uterus itself.

Some pathologists have ascribed the association of cancer with uterine fibroids to "irritation," excited by the presence of the latter and the consequent hyperplasia of the mucosa.

Thorn [1] has reported an instance of this kind, in which the cancerous disease appeared to have been caused by the presence of a large calcified fibroid. If this alleged causation were of common occurrence, we should expect to find fibro-myomata more often concomitant with uterine cancer, than with any other local variety of cancerous disease.

But this is not so, for myomata coexist with uterine cancer only in 9 per cent. of the necropsies ; whereas, I have found that they coexist with cancer of other localities, to the extent of 18·5 per cent.[2] It is evident, therefore, that the changes excited in the uterine mucosa etc., by the presence of myomata, do not specially predispose to cancer.

Passing now to the consideration of the alleged proclivity of uterine myomata to become *sarcomatous*, the first fact that strikes me is, the great frequency of the former and the great rarity of the latter disease. My analysis of 2,649 consecutive cases of uterine neoplasms shows 883 uterine fibro-myomas, and only 2 sarcomas. In Gurlt's analysis of 4,115 uterine neoplasms, the proportion of fibroids to sarcomas is as 481 to 8.

It is evident from these data, that uterine myomata seldom become sarcomatous.

This is quite in accord with the experience of operators, who have found that only from 2 to 4 per cent. of their cases were complicated by sarcoma. Of course, even this proportion of malignant cases, is far in excess of the average for myomata in general ; for, the cases comprised in this estimate, were specially selected as requiring operative treatment.

Among those who have recorded series of cases of this kind, reference may be made to Evelt's [3] table of 120 operations, with 3 examples of sarcoma ; to Fleischmann's [4] 130 cases, with 5 examples of sarcoma ; to Hauber's [5] 138 operations, with 3 examples of sarcoma ; to Ulesko-

[1] *Zeits. f. Geb. u. Gyn.*, 1893, Bd. xxviii., Heft 1.
[2] Of 44 breast-cancer necropsies, I found uterine fibroid in 5 ; and of 37 necropsies for cancer in other localities fibroids were present in 10 cases.
[3] *Monats. f. Geb. u. Gyn.*, November, 1903.
[4] *Wien. med. Woch.*, 1906, Bd. lvi.
[5] *Zent. f. Gyn.*, 1904, No. 11.

Stroganowa's [1] 100 cases, with 10 instances of malignant disease; to Hunner's [2] 100 cases, with 7 examples of malignancy; to Cullingworth's [3] 100 cases, with 1 example of malignancy; to Flatau's [4] 104 operations, with 5 instances of sarcoma; to Fehling's [5] series of 409 operations, with 9 sarcomata; to Martin's [6] 205 cases, with 4 sarcomata etc.: thus, of these 1,406 operated myomata, 39 or 3·3 per cent. were sarcomatous.

I have seen it stated, that cystic myomata are more prone to originate sarcoma than their solid congeners; but, I believe this is due to cystic sarcomata and myomata, being easily mistaken for true cystic myomata.

It is thus quite clear, that the origin of sarcomatous disease from myomatous tumours, is very much rarer than it would be, if these tumours really had any special proclivity that way.

Nevertheless, the fact of the occasional origin of sarcomatous disease in uterine fibro-myomata, has been clearly established by many well-recorded examples.

In this connexion, it must be remembered that myomata are of composite build, including connective tissue, muscle elements, bloodvessels, and lymphatics, any of which may be comprised in the sarcomatous matrix. Hence corresponding varieties of the disease. Thus, when the morbid process centres in the connective tissue, its elements multiply, destroying the adjacent fibrous tissue, muscle cells etc. (*myosarcoma, myomyxoma* etc.); when the bloodvessel and lymphatic elements are chiefly involved, we get telangiectasic (*myosarcoma telangiectaticum*), and lymphangiectasic varieties (*myosarcoma lymphangiectaticum*). In other instances the muscle elements are alleged to be primarily affected, and to increase at the expense of the remaining constituents (*myoma levicellulare malignum*). In their recurrences and metastases, each of these varieties usually breeds true.

The occurrence in these tumours of cartilaginous, osseous, and other heterotopic structures, of which many instances have now been reported (Ascher, Feuchtwanger, Kworostansky, Freund, Bidder etc.), seems to indicate that this form of sarcomatous disease may often be of pre-natal origin.

Myomata of the uterine wall may also, very rarely, be secondarily invaded by sarcomatous disease of the overlying mucosa, of which Whitridge Williams has reported an instance.

It follows from what has been stated, that the possibility of benign uterine tumours taking on malignant characters cannot be denied; but this is a very different thing from admitting, that such neoplasms are specially prone to become malignant. This is disproved by the great rarity of the coincidence. Non-malignant uterine tumours, have no special proclivity to malignant disease; on the contrary, as I have shown, they are much less prone to originate such changes, than are the morphological elements of the uterus itself.

[1] *Monats. f. Geb. u. Gyn.*, September, 1902.
[2] *Am. Med.*, July 11, 1903.
[3] *British Journal of Obstetrics and Gynæcology*, January, 1902.
[4] *Münch. med. Woch.*, 1901, No. 14.
[5] *Beitr. z. Geb. u. Gyn.*, 1898, i., S. 485.
[6] *Arch. f. Gyn.*, 1888, Bd. xxxii., S. 470.

### Mammary Adenoma and Malignant Disease.

After the non-malignant adenomata ("chronic mammary tumours") had been clearly differentiated from malignant tumours of the breast by Astley Cooper, the partisans of the old belief as to the special proclivity of the former to become malignant, still persisted in the old creed. Cooper himself admitted the possibility of such an occurrence, thus he says:[1] "I believe that if a person has a tumour of the breast which is not malignant, and that it remains so till the change of life takes place; that then an undue action may be excited in the part, and the tumour become scirrhous."

In order to determine the ratio in which epithelial cancer arises from non-malignant mammary tumours, I have consulted the records of 254 consecutive cases of mammary cancer, of which I have preserved detailed reports: I find that, in this series, cancer originated in connexion with fibro-adenoma in only two instances. In other words, for every case of cancer that had originated, under circumstances suggestive of its having sprung from a fibro-adenoma, there were 126 cases that had evidently originated otherwise.

Now I have ascertained that the relative frequency of the occurrence of fibro-adenomatous and cancerous tumours in the female breast is 372 to 1,863, or the ratio is about 1 to 5.

It is evident from these data, that the malignant transformation of fibro-adenomata is an event of extreme rarity—very much rarer than it would be, if fibro-adenomata had any special proclivity to become cancerous.

Even when mammary carcinoma is found in association with a non-malignant tumour of the part, the cancerous disease often appears to have originated quite independently of the latter, as in cases reported by Paget,[2] Bryant,[3] Richet,[4] Gross,[5] Waldeyer[6] and others. I have met with, and elsewhere described,[7] two somewhat similar cases.

Many instances of the origin of *sarcoma* in association with mammary fibro-adenoma, have now been recorded. Some authors even maintain, that most sarcomata of the breast arise in this way, rather than from the tissues of the gland itself; thus, of eight cases specially studied by Labbé and Coÿne[8] *ad hoc*, four of them appeared to have originated from old adenomata. I have not met with such cases in anything like such a large proportion; for, among thirty sarcomata of the breast specially studied by me, there was only one instance in which the malignant affection arose in this way. Hence, I feel bound to reject Labbé and Coÿne's conclusion, which appears to be based upon too narrow an experience. In some of these chronic mammary tumours, we probably

[1] "Lectures on Surgery," 1839, p. 378.
[2] "Lect. Surg. Path.," 1853, vol. ii., p. 259.
[3] "Diseases of the Breast," 1887, p. 339.
[4] *Le Practicien*, 1879, No. 14, p. 163.
[5] "Am. Syst. Gyn.," vol. ii., p. 207.
[6] *Arch. f. path. Anat.*, Bd. lv., S. 124.
[7] "Diseases of the Breast," p. 312.
[8] "Traité des Tumeurs bénignes du Sein," pp. 290 and 365.

have to do with sarcomatous disease, starting from overgrown supernumerary mammary sequestrations, as I have elsewhere indicated.[1]

From what has been stated, it may be concluded that non-malignant mammary tumours, like their uterine congeners, have no special proclivity to originate malignant disease.

### Ovarian Cystoma and Malignancy.

The question of the frequency of malignancy, as a complication of ovarian cystomata, has been much debated among practitioners; but, as the matter has seldom been studied with the aid of adequate statistical data, very little has been done to dissipate the prevailing obscurity and confusion.

In approaching this tangle with the object of getting at the truth, the first item that strikes me, is the great frequency of these non-malignant ovarian cysts; and the great rarity of any form of malignant disease of ovarian origin.

For instance, of 9,701 cases of tumours in women, under treatment at several of the chief London general hospitals during a succession of years, I found that 4,036 had non-malignant tumours, of which 635 were ovarian cysts, or 6·5 per cent. of the total; whereas, 5,665 had malignant tumours, of which only 67 were ovarian, or 0·69 per cent. of the total.

Gurlt's analysis[2] of 7,776 cases of malignant disease in women at the chief Vienna hospitals, points to the same conclusion; for, in only 78 of these patients, or in 1 per cent., did the disease originate in the ovary.

If further evidence as to the comparative rarity of malignant disease of the ovaries is required, reference may be made to the national mortality returns; thus, the Sixty-third Annual Report of the Registrar-General, shows that of 15,588 women who died of malignant disease during the year 1900, the ovary was the part affected in 275 cases, or in 1·7 per cent.; and the United States national statistics for the same year, show a still smaller proportion of malignant ovarian disease—viz., less than 1 per cent. (0·9).

The obvious inference from these data is, that non-malignant ovarian cystomata seldom originate malignant disease, and this conclusion accords with the clinical evidence, as furnished by the record of long series of operated cases by individual surgeons: thus, of 1,388 ovarian tumours operated on by the surgeons of the Johns Hopkins Hospital, Swan found that only 41 were malignant, or about 3 per cent.; and Geyer, for the Würtzburg clinic, gives the percentage of malignancy as 2·3.

Here it seems desirable to point out that ovarian cystomata comprise several different varieties of tumours, among which it is in this connexion, necessary to discriminate and set aside for separate consideration, the papilliferous and dermoid forms.

It may be taken as proved, that malignant disease may exceptionally arise from each of the different varieties of cystomata; but, some of them appear to have greater proclivity in this direction than others.

[1] "Diseases of the Breast," p. 73, etc.
[2] *Arch. f. klin. Chir.*, 1880, Bd. xxv., S. 420.

The papilliferous ovarian tumours—or at any rate a considerable proportion of them—are marked off from the other varieties, by the fact that they manifest contagious properties,[1] that is to say, they often become diffused throughout the peritoneal sac by auto-implantation of detached fragments; hence their recurrence after removal *in situ*, or in some part of the operation wound, is frequent. Moreover, the disease is generally bilateral—in over 68 per cent. of the total cases, according to Pfannenstiel. It is necessary to distinguish this form of local diffusion, from the very different generalization of malignant disease, with which it is undoubtedly often confounded. It is probably owing chiefly to this cause, that papilliferous ovarian tumours have acquired a special reputation for malignancy;[2] and the fact that primarily-arising ovarian cancer, sometimes assumes the papillary form *ab initio*, has tended to the same end.

When due allowance has been made for these sources of error, it is doubtful whether there is any justification for the general belief, in the special proclivity to malignancy, of these papilliferous tumours. The researches of Pfannenstiel,[3] Semb[4] and others, specially point to this conclusion; with which the fact that papillomata in general, manifest no such proclivity, also accords.

The rather numerous cases reported in comparatively recent times, of the supervention of malignant disease—in both its epithelial and connective tissue forms—in connexion with dermoid and teratoid ovarian tumours, suggest that these formations may have special proclivity that way; but, in the absence of the requisite numerical data, nothing more definite can be said.

With regard to the other and commoner varieties of ovarian cysts, which after all comprise the great majority, there is a consensus of opinion, that they have no special proclivity to malignancy; and this accords with the data revealed by my statistical research, as previously mentioned. When therefore it is stated that, from a practical standpoint, "all ovarian tumours must be regarded as malignant until removed and proved otherwise," I reply that, although this may be "a very convenient doctrine for surgeons," it is certainly not in conformity with the facts revealed by a scientific examination of the subject.

In other parts of the body, where I have specially studied the question, I have found that this conclusion is equally valid.

In like manner Semon[5] reports, that of 10,747 non-malignant, intra-

[1] The ensemble of the characters of these growths indicate their affinity with the genital condylomata; and, like the latter, they are probably transmitted during sexual intercourse, either with or without some other venereal malady, such as gonorrhœa, syphilis, etc. To this it may be objected that, although growths of this kind are recognized as occurring in the vagina, portio, and tube, they have never been met with in the uterus. The answer is that these lesions also occur in the uterus, where they are commonly confounded with certain hypertrophic forms of chronic endometritis, adenoma, and even, in rare cases, with villous cancer, etc. In this connexion we must remember that it is only in comparatively recent times—thanks to the publications of Doran, Doleris, etc.—that the occurrence of similar papillomatous growths in the Fallopian tubes has been discriminated; and even now the identity of the latter with condylomata is not recognized by gynæcologists.

[2] Gebhard, "Path. Anat. d. weibl. Sexualorgane," 1899, S. 356.

[3] Veit's "Handb. d. Gynäkologie," 1898, Bd. iii.

[4] *Norsk. Mag. f. Laegeridensk*, October, 1896.

[5] *Cent. f. Chir.*, 1890, S. 463.

laryngeal neoplasms, whose history had been studied by him, there were only 47 instances in which malignant disease had supervened.

It follows from what has been stated, that the possibility of benign tumours subsequently developing malignant characters, has been thoroughly proved; but this is a very different thing from admitting that such tumours are specially prone to malignancy. This is disproved by the extreme rarity of the coincidence. Non-malignant tumours are, in fact, less liable to originate malignant disease, than are the normal morphological elements of the body itself.

## CHAPTER XIII

## MULTIPLE PRIMARY CANCER; AND THE ASSOCIATION OF CANCER WITH OTHER TUMOURS

A PECULIAR feature of cancer is, that the initial lesion is generally solitary. The researches of Hauser and Petersen into the architecture of small cancerous nodules, by serial sections and reconstruction models, show that the disease spreads in a multicentric manner, each ingrowing column being an outgrowth from the original germ, and therefore at first continuous with it. It is now, however, generally recognized, that exceptionally the disease springs up from more than a single original germ; and it is this that constitutes primary multiplicity, as the term is here employed.

Pathologists have been aware of this for some time, although it is only recently that the subject has attracted special attention. Such cases, however, are decidedly rare.[1] The wonder is that they do not occur more frequently, especially if—as alleged—cancer is a parasitic disease. By some, however, this peculiarity has been taken to indicate analogy with certain specific diseases, the virus of which—when introduced into the system—confers immunity for a longer or shorter period. The ensemble of the indications, as previously mentioned, is, however, decidedly against the acceptance of this suggestion.

Such indications seem to me rather to imply, that the solitariness of the initial lesion of cancer is, in its origin, akin to the solitariness of most non-malignant tumours, and developmental anomalies *per excessum.*

At any rate, it is worth noting in this connexion, that all non-malignant tumours are occasionally multiple in origin; and some of them, such as uterine myomata, frequently manifest initial multiplicity.

### Bilateral Manifestations.

Among the numerous cases of the multiple outbreak of malignant disease lately reported, some of the most striking are those in which the malady arises concurrently in both of paired organs, or in both of other bilaterally symmetrical parts of the body. These bilateral tumours are often described as symmetrical: but, it is very seldom that the concomitant tumours correspond so exactly, as to justify the use of this term.

[1] Of 1,664 cases of mammary cancer tabulated by Gross, only 2 were bilateral in origin; but Billroth met with 3 instances of this kind in 245 mammary cases; according to Nicholls, of 685 necropsies for cancer in Montreal hospitals, 18 showed initial multiplicity.

A considerable proportion of bilateral malignant tumours are met with in early life, and are of congenital origin, many of these obviously arising in connexion with gross developmental lesions. In other cases of this kind, there is often evidence of the malignant disease having supervened on some antecedent morbid condition, such as eczema, seborrhœa etc.

Non-malignant tumours of bilateral origin, are even less exceptional than their malignant congeners.

Of course care must be taken to discriminate these primarily arising bilateral malignant tumours, from secondary forms, due to bilateral dissemination from a remote primary source, *e.g.*, stomach, thyroid, prostate etc., as also from local disseminative lesions, whether continuous or discontinuous; and this is sometimes by no means easy.

Subjoined I submit a few remarks, as to the leading features of some of the chief local varieties of these bilateral outbreaks.

**Mamma.**—I have elsewhere described [1] an example of bilateral cancer of the female breast; and referred to similar cases by Aitken, Volkmann, Klotz, Terrillon and others. In all of these instances, the malady was concomitant with the puerperal state, its onset was acute, and its progress very rapid; hence Klotz has described the condition as "*Mastitis carcinomatosa gravidarum et lactantium.*" Billroth [2] has described an instance of acute bilateral sarcomatous disease of the breast, in a pregnant woman. This type of malignant disease seems to be relatively less rare than the epithelial form; for, of Gross's 156 cases of mammary sarcoma, 3 were bilateral.

Mammary fibro-adenomata may also be bilateral, for of 46 cases studied by me, in 1 instance there were several small tumours in both breasts; and of Velpeau's 54 cases, 5 were bilateral.

It is by no means rare to see cancer of one breast followed, after a time, by outbreak of the disease in the other. The great majority of these cases are, however, due to direct extension of the primary disease, or to its dissemination. Yet it occasionally springs up independently in the opposite breast; and I have elsewhere [3] reported a case of this kind.

I have also there cited several remarkable instances in which, many years after extirpation of one breast for cancer without recurrence, the disease subsequently supervened in the opposite breast.

Other instances of bilateral malignant disease of the breast, in which the concomitant tumours were of different anatomical structure, may also be mentioned in this category.

Thus, Lebert [4] long ago described an example of colloid cancer of one breast, concomitant with ordinary scirrhus of the other.

In like manner, Nunn [5] has met with tubular cancer of the left breast, coexisting with atrophic acinous cancer of the right breast: Mandry [6] and Küster [7] have had similar finds.

Instances of scirrhous cancer of one breast, concomitant with sarcoma

[1] My book on "Diseases of the Breast," 1894, p. 318.
[2] *Deutsche Chir.*, Lief. xli., S. 27. [3] "Diseases of the Breast," 1894, p. 302.
[4] *Arch. f. path. Anat.*, Bd. iv., S. 216.
[5] Transactions of the Pathological Society, London, 1890, vol. xli., p. 224.
[6] *Beitr. z. klin. Chir.*, 1892, Bd. viii., S. 589.
[7] Cited in Michelsohn's Inaug. Diss. "Zur Multiplicität der primären Carcinomen," Berlin, 1889.

of the other, have been described by De Morgan, Czerny, Bryant, and Billroth.[1]

**Ovary.**—Malignant tumours of the ovaries are often bilateral in origin. This is especially the case with sarcomatous kinds, a large proportion of which occur in early life : thus of 23 ovarian sarcomata studied by Pick, 9 were bilateral—of which latter, 6 were of the small round-celled variety. Examples of bilateral glandular ovarian cancer have been studied by Woolley,[2] Nicholls,[3] and others ; while, in a patient aged seventy, Frangenheim [4] met with glandular cancer of both ovaries, together with endothelioma of the dura mater. Here also mention may be made of Ladinski's [5] remarkable case of glandular cancer of one ovary, with sarcoma of the other, in a patient with absence of the uterus, vagina, and tubes.

Examples of the development of cancer in the sound ovary, after the removal of its cancerous fellow, have been reported by Le Gemtel [6] and others.

With regard to the initial multiplicity of non-malignant ovarian tumours, I need only mention that it is of frequent occurrence, especially in the dermoid, papillary and cystic forms.

Here it seems desirable to mention, that bilateral malignant ovarian tumours are fairly often met with, as the result of dissemination from primary growths situated in the stomach, intestines, other abdominal viscera etc. ; and it is probable that some of the bilateral ovarian growths, called " Krukenberg's tumour," are really of this nature.

In this connexion it should also be borne in mind, that secondary malignant ovarian disease is relatively much more frequent than the primary form, especially in adults. On the other hand, post-mortem records show, that gastro-intestinal cancers seldom disseminate in the ovaries.

**Testis.**—It is by no means very rare, for malignant tumours of the testis to be bilateral in origin ; and this seems to be of more frequent occurrence with the round-celled sarcomata, than with other forms of the disease.

A considerable proportion of these malignant testicular tumours, arise in infancy and early life ; and many of them are congenital.

In a remarkable congenital case reported by Rogers, both testes, which had not descended, were sarcomatous, causing a large intra-abdominal tumour, which proved a serious obstacle to delivery.

Malignant testicular tumours, especially those of early life, are remarkable for the great frequency with which heterotopic structures—such as cartilage, bone, striped muscle etc.—occur in them.

Of 15 early-life testicular malignant tumours tabulated by Schubert, 3 were bilateral ; and of 93 cases—mostly adults—analysed by Kober, 5 were bilateral.

[1] For abstracts, *vide* my book on " Diseases of the Breast," p. 307.
[2] *Boston Medical and Surgical Journal,* 1903, No. 1, p. 1.
[3] *Montreal Medical Journal,* 1903, p. 326.
[4] *Arch. f. path. Anat.,* 1906, Bd. clxxxiv., S. 201.
[5] *American Journal of Obstetrics,* July, 1898.
[6] *Bull. et Mém. Soc. Anat. de Paris,* 1906, No. 6, p. 470.

**Kidney.**—Malignant tumours of the kidney are decidedly rare, except in infancy and early life, when many cases are met with, a considerable proportion of which are congenital, and bilateral in origin. As previously mentioned,[1] it was by studying a case of a bilateral renal sarcoma in a young infant, that the "rest" theory of tumour formation was suggested to Cohnheim. According to Paul,[2] about half of these early-life renal sarcomata are bilateral; but Walker,[3] from an analysis of 141 recorded cases, finds that this proportion of bilateral cases is much too high, only 10 of his cases being bilateral.

Bilateral origin is, however, of much more frequent occurrence in early-life sarcomata, than in any of the malignant renal tumours of more advanced life, although bilateral forms of the disease are occasionally met with even then; thus, in an epileptic, male idiot, aged forty-four, Scheren[4] found a sarcomatous "mixed" tumour of each kidney, together with cylinder-celled cancer of the stomach, and multiple psammo-sarcoma of the brain.

**Adrenal.**—In infants and adults bilateral forms of malignant adrenal tumours are occasionally seen: Rolleston and Marks, in 26 tabulated cases at all ages, met with 2 instances of this kind.

A case, which conclusively proves the bilateral origin of the disease, had been recorded by Breton and Looten.[5]

The patient, a woman aged fifty-seven, having suffered for some time from symptoms of adrenal insufficiency, with a painful intra-abdominal tumour, died suddenly. At the necropsy, each adrenal was enormously enlarged by small round-celled sarcomatous growth, which had secondarily invaded and caused enlargement of, each corresponding kidney, and the adjacent mesenteric glands. No other organs were involved. Similar cases have been reported by Fränkel,[6] Woolley,[7] Suchardt and others. Adenoma of both adrenals has also been met with.[8]

**Eye.**—Choroidal sarcomata are occasionally bilateral: this was so in 5 of 214 cases studied by Fuchs.

With glioma of the retina bilaterality is of more frequent occurrence, and many congenital cases of this kind have been reported—indeed, congenital glioma is usually bilateral. Of 60 cases of glioma retinæ analysed by Lawford and Collins, in 12 the disease appeared to be bilateral in origin; of Hirschberg's 60 cases, 14 were bilateral; and of Wintersteiner's 405 cases, 97 were bilateral.

Brault has met with bilateral congenital ocular lipoma.

**Ear.**—Instances of the bilateral outbreak of epithelioma of the external ear, have been described by Mandry[9] and Sumpter.[10] In the latter's patient, "cancer" of the lip had been extirpated nine years previously, without recurrence. In all these cases the malignant disease supervened on chronic eczema of the part.

[1] Chapter VII. [2] *Liverpool Med.-Chir. Journal*, January, 1898.
[3] *Annals of Surgery*, 1898, vol. xxvi., p. 529.
[4] Cited by Walter (*Arch. f. klin. Chir.*, 1896, Bd. 53).
[5] *Le Nord. Méd.*, August 15, 1905. [6] *Arch. f. path. Anat.*, Bd. ciii., S. 244.
[7] *Boston Medical and Surgical Journal*, 1903, No. 1.
[8] Warthin, *Arch. of Pediatrics*, 1901, p. 812.
[9] *Beitr. z. klin. Chir.*, 1892, Bd. viii., S. 589.
[10] *Lancet*, 1893, vol. i., p. 887; also *ibid.*, 1894, vol. i., pp. 1160 and 1274.

**Extremities.**—Of 263 cases of primary cancer of the extremities analysed by Michael,[1] two were bilateral and approximately symmetrical: in one of these cases the cancerous disease supervened on chronic varicose ulcers.

Massen has reported bilateral congenital myxosarcoma of the gluteal region.

It is evident from these notes, that the bilateral outbreak of malignant disease in paired organs, is less exceptional than is generally believed, even when liberal allowance has been made for possible sources of error.

### Other Examples of Primary Multiplicity.

**Skin.**—In no part of the body does the initial outbreak of cancer, so frequently manifest itself in the form of multiple foci, as in the skin—especially the skin of the face. In these cases, hyperplastic changes of the integument or other lesions, almost invariably coexist; and workers in certain irritating substances such as tar, paraffin, soot etc., are relatively often affected.

I have elsewhere[2] described the case of an asphalter, aged seventy-two, with three widely-separated, independent cancerous lesions on different parts of the face, associated with "chronic seborrhœa."

Two of these lesions were ordinary epidermoidal cancer, while the third was cylinder-celled, sweat-gland cancer.

Similar cases have been reported by Volkmann,[3] Tillmanns,[4] Schimmelbusch,[5] and others. In chimney-sweeps I have seen the scrotal integument similarly affected. Tillmans has met with an instance of epithelioma of the integument of the forearm and of the scrotum, in a paraffin worker. In old persons, multiple cutaneous cancers sometimes arise in connexion with chronic seborrhœa. Primary multiplicity is also often met with in cases of rodent ulcer,[6] especially in aged subjects; and Bowlby[7] has seen six distinct lesions of this kind in one patient.

Examples of multiple cancer of the skin of the face, supervening on lupous ulceration, have been recorded by Steinhauser, Bayha and others. It will be noticed that in most of the cases just mentioned, the outbreak of the cancerous disease appears to have been precipitated by some form of antecedent lesion; which, it may be surmised, acted as fuel to the fire of pre-existing epithelial proliferation.

Schimmelbusch has described epidermoidal cancer of the skin of the nape of the neck, concomitant with the same kind of cancer of the skin of the ear; also the same kind of cancer of the ear and lower lip.

Tillmanns, in like manner, found the skin of the scrotum and forearm concurrently affected; and C. Thompson[8] the skin of the scrotum, thigh and calf of one leg. Beatson[9] met with rodent ulcer of the face, in

[1] *Beitr. z. klin. Chir.*, Bd. vii., S. 13.
[2] *Twentieth Century Practice of Medicine*, 1898, vol. xvii., p. 228.
[3] *Sam. klin. Vorträge*, No. 257. [4] *Deutsche Zeits. f. Chir.*, 1880.
[5] *Arch. f. klin. Chir.*, 1880.
[6] For cases, *vide* Hutchinson's "Archives of Surgery," 1891, vol. iii., pp. 318 and 335.
[7] Transactions of the Pathological Society, London, 1894, vol. xlv., p. 163.
[8] *Practitioner*, October, 1899, p. 414.
[9] *British Medical Journal*, 1899, vol. ii., p. 1602.

association with epidermoidal cancer of the skin of one hand, and cutaneous papilloma of the other hand; Winiwarter,[1] three years after excision of epidermoidal cancer of the lower lip, without recurrence, found cutaneous cancer of the root of the nose; and Becker[2] met with rodent ulcer of the left ala nasi, and similar disease of the right ear, together with melano-sarcoma of the right cheek, the patient being also affected with congenital angioma of the left cheek, pigmented hairy mole of the forehead, as well as with comedones, chronic seborrhœa, acne of the face etc.

Many examples of primary multiple sarcoma of the skin have also been recorded in children and adults, several of the former being congenital (Karewski etc.); but, the whole subject of sarcoma of the skin, and its relation to other morbid conditions, is in such a confused and unsatisfactory condition, that I must be excused from entering further into the matter here.

As examples of the outbreak of the disease concurrently in the integument and other parts of the body, the following cases may be mentioned:—epidermoidal cancer of the skin of the foot, with columnar-celled cancer of the gastric mucosa by Cordes;[3] epidermoidal cancer of the skin of the abdomen, and cancer of the pyloric mucosa by Hutchinson;[4] I have seen rodent ulcer of the face, in a man from whose lower lip epidermoidal cancer had been excised fifteen years previously, without return of the original disease; cancer of the stomach, in a man whose ear had previously been extirpated for epidermoidal cancer, by Billroth;[5] epidermoidal cancer of the skin of the face, with spheroidal-celled cancer of the pyloric mucosa, by Klebs;[6] epidermoidal cancer of the skin of the upper eyelid, with cylinder-celled cancer of the rectal mucosa, by Kaufmann;[7] rodent ulcer of the face of fourteen years' duration, with sarcoma of the antrum of the superior maxilla by Langton[8] etc.

**Uterus.**—In the uterus, as in most other parts of the body, the initial manifestation of cancer is nearly always solitary; but a few instances of primary multiplicity have lately been recorded.

Thus Hofmeier, Winter, Schauta and Binswanger have reported cases, in which epidermoidal cancer of the portio, was concomitant with cylinder-celled glandular cancer of the corpus or cervix; John Williams met with an instance, in which two separate columnar-celled glandular cancers of the canalis cervicalis, were associated with epidermoidal cancer of the portio; while Hitschmann, Kaufmann, Lewers and others have found epidermoidal cancer of the corpus (including ingrowths and "nests"), combined with cylinder-celled adeno-carcinoma of the same part.

The infantile type of uterine sarcoma is generally congenital, and multiple *ab initio;* and, even among adult forms of uterine sarcoma, primary multiplicity is occasionally seen, especially in those of mucosal origin.

Examples of concomitant uterine epithelioma and sarcoma, have

[1] "Beitr. z. Stat. d. Carcinom.," 1878. [2] *Beitr. z. klin. Chir.*, Bd. xiv., S. 146.
[3] *Arch. f. path. Anat.*, 1896, Bd. cxlv., S. 422.
[4] "Archives of Surgery," vol. iii., p. 47.
[5] Cited by Mercanton (*Rev. Méd. de la Suisse rom.*, 1893, No. 3, p. 173).
[6] *Arch. f. path. Anat.*, Bd. cxl. [7] *Ibid.*, 1879.
[8] St. Bartholomew's Hospital Reports, 1888, vol. xxiv., p. 284.

been recorded by Montgomery, Niebergall, Keller, Emanuel, Rabl-Rückhardt, Franqué and others.

In Montgomery's[1] case, cancer of the cervix was associated with sarcoma of the corpus; while in Niebergall's,[2] both forms of malignant disease were present in the corpus, together with myoma and mucosal polypi. Milford[3] had previously described an instance of concomitant melanotic, myxomatous, myomatous and cystic uterine tumours.

I have elsewhere[4] given examples of multiple malignant uterine growths, due to the spread of the disease by auto-implantation and dissemination.

Cases illustrating the independent outbreak of cancer in the breast and uterus, have been carefully studied by Richter,[5] Beadles,[6] Young,[7] Mercanton[8] (three cases), Broca[9] etc.

Richter's and Beadle's patients were concurrently affected with epidermoidal cancer of the cervix uteri, and acinous glandular cancer of the mamma. In a case of this kind by Walter,[10] ovarian cystoma was also present.

Russell (of Baltimore[11]) has described cases in which—after vaginal hysterectomy for cancer without local recurrence—cancer of the breast subsequently developed independently.

The independent outbreak of cancer in the breast, uterus, and ovary has been signalized by Walter;[12] in the vulva, breast and uterus by Zeiss;[13] in the uterus and vagina by Mercanton;[14] in the uterus and vulva by Mercanton; in the uterus and Fallopian tube by Hafbauer;[15] in the uterus and ovaries by Reichel[16] and others; in the uterus (epidermoidal cancer of the cervix) and pancreas (cylinder-celled glandular cancer) by Bard;[17] the same variety of uterine cancer, concomitant with cylinder-celled cancer of the sigmoid colon by Beck;[18] in the uterus (epidermoidal cancer) and thyroid (adeno-carcinoma) by Richter;[19] in the uterus and stomach by Walshe,[20] Krönig[21] etc.

An elderly lady, one of whose eyes had been extirpated by Hutchinson[22] for melanotic sarcoma, died—free from any return of the original disease—ten years afterwards, of cancer of the uterus.

Hanot[23] found cancer of the liver, coexisting with sarcoma of the uterus; Schmincke,[24] cylinder-celled cancer of the gall-bladder, likewise with sarcoma of the uterus; and Luminezen sarcoma of the vagina, with epithelial cancer of the uterus.[25]

**Mamma.**—An example of epidermoidal cancer of the nipple, with

[1] *Occidental Medical Times*, 1893, p. 311. [2] *Arch. f. Gyn.*, Bd. l., Heft 1, S. 129.
[3] *New South Wales Medical Gazette*, 1873-1874, vol. iv., p. 163. [4] Chapter VIII.
[5] *Wien. klin. Woch.*, August 17, 1905, S. 865.
[6] Transactions of the Pathological Society, London, 1897, vol. xlviii., p. 236.
[7] *Archives of the Middlesex Hospital*, 1904, vol. iii., p. 165.
[8] *Rev. Méd. de la Suisse Romande*, 1893, No. 3, p. 173.
[9] "Traité des Tumeurs," 1866, t. i., p. 284. [10] *Arch. f. klin. Chir.*, 1896, Bd. liii.
[11] *Johns Hopkins Hospital Bulletin*, December, 1899. [12] *Op. cit.*
[13] *Cent. f. Gyn.*, 1892, No. 40. [14] *Op. cit.*
[15] *Arch. f. Gyn.*, Bd. lv., S. 316. [16] *Zeits. f. Geb. u. Gyn.*, 1880, Bd. xv.
[17] *Arch. gén. de Méd.*, 1892, p. 541. [18] *Prag. med. Woch.*, 1883.
[19] *Op. cit.* [20] "Nature and Treatment of Cancer," 1846.
[21] *Cent. f. Gyn.*, 1902, No. 30. [22] *Archives of Surgery*, vol. iii., No. 9, p. 48.
[23] Cited by Bard. [24] *Arch. f. path. Anat.*, 1906, Bd. clxxxiii., S. 160.
[25] *Pest. med. chir. Presse*, 1878, xiv., p. 176.

concomitant acinous glandular cancer of the same breast, has been recorded by Morestin;[1] and some cases of so-called "Paget's disease," undoubtedly belong to the same category.

In a single breast, mixed malignant tumours—comprising sarcomatous and epitheliomatous elements—have also been reported (Heurtaux, Coen etc.), to which reference has been made in a previous chapter.[2]

I have elsewhere[3] recorded the case of an elderly woman who, having suffered for seven years from "rodent ulcer" of the face, then developed cancer of the mammary gland. She was also subject to uterine myomata. Hutchinson[4] has met with similar cases of the concomitancy of mammary cancer with rodent ulcer of face.

Bryant[5] and Michelsohn[6] have seen scirrhous cancer of the breast, concomitant with epidermoidal cancer of the nose (three cases); and the former has met with cancer of the breast associated with œsophageal epithelioma.

Panas[7] mentions the case of a man with scirrhous cancer of the breast, from whose lower lip epithelioma had been excised fifteen years previously; and similar cases have been recorded by Young and Winiwarter; while Graviller[8] has seen cancer of the male breast, concomitant with epidermoidal cancer of the lower lip.

A patient of Dobson's,[9] who had remained well and free from any return of the disease for six years after amputation of the breast for cancer, then developed epidermoidal cancer of the tongue, of which she soon died; another patient of the same surgeon, two years after extirpation of the breast for cancer, of which there was no return, died of small round-celled sarcoma of the tonsil.

Gibson[10] has recorded the case of an old woman, who died of cancer of the pylorus, more than twenty years after extirpation of the right breast for cancer; Poulsen's patient died of cancer of the stomach, five years after extirpation of the breast for the same disease; Nicholls[11] has described cancer of the pyloric mucosa, with acinous glandular cancer of the mamma; and Fraenkel[12] acinous cancer of the left mamma, with cylinder-celled cancer of the colon.

Guende[13] met with sarcoma of the choroid in a woman, the subject of mammary cancer; Nehrkorn[14] sarcoma of the vagina, with mammary cancer; and Schael[15] scirrhus of the mamma, with spindle-celled sarcoma of one ovary.

I have elsewhere[16] cited instances of associated mammary and ovarian cancer; Cutler[17] has met with cancer of various thoracic and abdominal

[1] *Arch. Gén. de Méd.*, April 21, 1903.
[2] Chapter VII.
[3] My book on "Diseases of the Breast," 1894, p. 304.
[4] *Archives of Surgery*, vol. iii., No. 9, p. 147.
[5] "Diseases of the Breast," 1887, p. 340.
[6] Inaug. Diss., Berlin, 1889.
[7] Cited by Poirier, "Tumeurs du sein chez l'homme," Paris, 1883, p. 98.
[8] *Canadian Medical and Surgical Journal*, Montreal, 1873, p. 271.
[9] *Bristol Med.-Chir. Journal*, December, 1889.
[10] *Lancet*, 1896, vol. ii., p. 225.
[11] *Montreal Medical Journal*, 1903, vol. xxxii., p. 326.
[12] *Münch. med. Woch.*, 1901.
[13] *Marseille Méd.*, 1890, No. 7, p. 326.
[14] *Münch. med. Woch.*, 1901.
[15] Cited by Wells (*Journal of Pathology and Bacteriology*, June, 1901).
[16] "Diseases of the Breast," 1894, p. 306.
[17] *Boston Medical and Surgical Journal*, 1892, p. 329.

organs, with sarcoma of the ovary; and Kesteven[1] found that cancer of the rectum and sarcoma of the femur developed in a patient, from whom recurrent mammary cancer had been extirpated six years previously, without any local recurrence.

**Gastro-intestinal Tract.**—Multiple primary malignant growths are met with more frequently in this system, than in any other part of the body, except the skin. I have previously referred to cases of multiplicity due to auto-implantation in this locality; and dissemination is another complication to be weighed, in estimating the validity of claims to initial multiplicity.

Instances of this kind have been reported as occurring in all parts of this tract, from the lips to the anus.

As examples, the following may be mentioned:—triple epidermoidal cancer of the tongue (Hayward and Henderson[2]); epithelioma of tongue, with sarcoma of epiglottis (Schiller[3]); double cancer of the œsophagus (Bucher[4]); epidermoidal cancer of the tongue, with double cancer of the œsophagus (Richter[5]); round and spindle-celled sarcoma with epidermoidal cancer, both of the lower part of the œsophagus (Frangenheim[6]); epidermoidal cancer of the tongue with columnar-celled (colloid) cancer of the jejunum (Abesser[7]); epidermoidal cancer of the œsophagus and stomach (Borst[8]); epidermoidal cancer of the œsophagus, with cylinder-celled cancer of the pyloric glands (Rosenbach[9]); epidermoidal cancer of the œsophagus, with cylinder-celled cancer of the ampulla of Vater (Courmont[10]); cylinder-celled cancer of the pylorus, with colloid cancer of the cæcum—two cases (Orth and Beck[11]); multiple cancer of the ileum (cases by Lubarsch[12] and Bunting[13]); multiple cancer of the jejunum (Notthaft[14]); cancer of ileum and lower part of the rectum—both of columnar type (Robson and Knaggs[15]); multiple cancer of the large intestine and rectum (cases by Rutherford, Teacher and Buchanan[16]); cylinder-celled cancer of the rectum and sigmoid colon—with multiple polypi (Morton[17]); cylinder-celled cancer of rectum and splenic flexure of colon—with multiple polypi (Handford[18]); cancer of the stomach and colon (Bucher[19]); double cylinder-celled cancer at opposite ends of the rectum, with multiple polypi (Robson and Knaggs[20]) etc.

The subjects of malignant disease of the gastro-intestinal tract, may also develop the malady independently in other parts of the body, of

[1] Clinical Society's Transactions, London, vols. vi. and ix.
[2] *Lancet*, 1901, vol. ii., p. 22.
[3] *Berlin. klin. Woch.*, 1898.
[4] *Ziegler's Beitr. z. path. Anat.*, Bd. xiv., Heft i., S. 100.
[5] *Wien. klin. Woch.*, 1905, S. 865.
[6] *Arch. f. path. Anat.*, 1906, Bd. 184.
[7] Cited in Michelsohn's I. D. "Zur Multiplicität der primären Carcinomen." Berlin, 1889.
[8] "Die Lehre von den Geschwülsten," 1902, Bd. ii., S. 773.
[9] *Arch. f. path. Anat.*, 1905, Bd. clxxix., S. 567.
[10] *Lyon Méd.*, April 15, 1894.
[11] Cited by Bard (*Arch. Gén. de Méd.*, 1892, i., p. 541).
[12] *Arch. f. path. Anat.*, 1888, Bd. cxi.
[13] *Johns Hopkins Hospital Bulletin*, December, 1904, p. 389.
[14] *Deutsche med. Woch.*, October 22, 1896.
[15] *Lancet*, 1905, vol. i., p. 640.
[16] Transactions of the Pathological Society, London, 1905.
[17] *Lancet*, 1895, vol. i., p. 1145.
[18] Transactions of the Pathological Society, London, 1890, vol. xlv., p. 133.
[19] *Ziegler's Beitr. z. path. Anat.*, Bd. xiv.
[20] *Op. cit.*

which many instances have been already cited in this chapter, and to these the following may be added :—cylinder-celled cancer of the mucosa of the colon with epidermoidal cancer of the vulva by Chiari ;[1] cancer of the pyloric mucosa with epidermoidal cancer of the skin of the right ear by Hauser ;[2] cancer of the colon, rectum and right adrenal by Zimmermann ;[3] colloid cancer of the cæcum, with epidermoidal cancer of the soft palate by Frangenheim ;[4] adeno-carcinoma of colon, with malignant cystoma of left ovary by Richter ;[5] carcinoma of stomach, with glioma of cerebrum by Hansemann ;[6] cylinder-celled cancer of the stomach, with spindle-celled sarcoma of one ovary, by Buchnell and Hinds ;[7] cancer of the stomach of " adenoid type," round-celled sarcoma of the right testis, with endothelial sarcoma of the dura mater ;[8] cancer of the stomach and bladder by Szumann ;[9] epidermoidal cancer of the œsophagus, with endotheliomata of the dura mater by Kretz ;[10] epidermoidal cancer of the œsophagus, with spindle-celled sarcoma of the stomach by Thierfelder ;[11] epidermoidal cancer of the anus, with villous cancer of the bladder by Nehrkorn ;[12] columnar-celled cancer of the rectum, with epidermoidal cancer of the larynx, has also been described by Butlin.[13]

Many examples of concomitant gastric and ovarian cancer have been reported ; as also of gastric cancer with ovarian fibro-sarcoma, endothelioma etc. (Krukenberg's tumours); intestinal cancer has also often been found associated with similar ovarian lesions : I have elsewhere [14] referred more fully to cases of this type.

Instances of the concomitant association of sarcoma of the choroid, with malignant epithelial tumours in other parts of the body, have been described by Parsons,[15] Fischer and Bosc.

From such examples as the foregoing, which by no means exhaust the list, the following conclusions may be drawn :—

1. The fact of the occurrence of multiple outbreaks of malignant disease is thus clearly established, both for individual organs, for paired organs, and for different parts of the body.

2. It is further established, that although primitively multiple malignant tumours are generally of the same kind ; yet, in many instances, they are generically different (*e.g.*, epithelioma and sarcoma) : and even when the multiple growths are of the same genus (*e.g.*, epitholioma) they may be of different varieties (*e.g.*, colloid cancer of one breast and scirrhus of the other etc.).

3. Multiple outbreaks of malignant disease are probably less exceptional than is generally believed, the evidence to this effect being especially strong in the case of paired organs.

[1] Cited by Bard.
[2] *Arch. f. path. Anat.*, 1894, Bd. cxxxviii., S. 402.
[3] *Canadian Journal of Medical Sciences*, Toronto, 1882, vol. vii., p. 390.
[4] *Arch. f. path. Anat.*, 1906, Bd. clxxxiv., S. 201.
[5] *Wien. klin. Woch.*, 1905, S. 865.
[6] *Zeits. f. Krebsforsch.*, i., p. 3, S. 183.
[7] *British Medical Journal*, 1905, vol. ii., p. 1115.
[8] Cited by Beadles (Transactions of the Pathological Society, London, 1897, vol. xlviii., p. 236).
[9] Cited by Bard.
[10] Cited by Walter (*Arch. f. klin. Chir.*, Bd. liii., 1896, S. 1).
[11] *Ibid.*
[12] *Münch. med. Woch.*, 1901.
[13] *British Medical Journal*, 1905, vol. ii., p. 1570.
[14] Chapter XIX.
[15] " Pathology of the Eye," 1905, vol. ii., p. 497.

4. Initial multiplicity is relatively often concomitant with certain structural derangements, which may be presumed to give predisposition thereto. These derangements comprise pre-natal developmental irregularities, especially obvious in the early-life, bilateral forms of multiplicity; local hyperplastic lesions, such as chronic seborrhœa, chronic eczema, lupus, and the effects of various irritants such as soot, tar, paraffin etc., especially obvious in cutaneous manifestations; in the gastro-intestinal system, such lesions as multiple polypi; and, in the breast, the puerperal state. In the uterus, conditions of this kind are less obvious; but they may, nevertheless, exist.

5. Taken in their entirety, these various considerations point to some general systemic change, as the predisposing cause of primary multiplicity.

### The Question of Mixed Malignant Tumours.

The question of the existence of mixed malignant tumours, that is to say, of tumours in which sarcomatous and epitheliomatous processes go on concurrently, is perhaps as yet hardly ripe for dogmatic treatment, by reason of the paucity of well-recorded facts relating thereto.

On *a priori* grounds, however, no objection need be raised to this conception; while some significant facts can be cited in its favour. Referring to this matter, Virchow [1] says: "There are true mixed forms of sarcoma and carcinoma—tumours of which certain parts are sarcomatous, while others are carcinomatous."

In support of this dictum, reference may be made to several cases in the foregoing list, in which two different kinds of malignant growth were found concurrently in certain organs, either as two separate tumours, or more or less fused into a single tumour (sarco-epithelioma).

Thus, in Frangenheim's case, we see at the lower end of the œsophagus a round- and spindle-celled sarcoma, and so closely contiguous to it as to form but a single morbid mass—epidermoidal cancer.

Then, in the mamma, we have instances in which the two kinds of malignant disease are so closely combined, as together to form but a single tumour, as in Heurtaux's case of glandular cancer with ossifying and chondrifying sarcoma, which I have elsewhere [2] fully detailed; moreover in this case, the secondary growths reproduced all the peculiarities of the primary mixed tumour.

In other parts of the body similar instances have been reported, especially in connexion with the malignant tumours of infancy and early life: thus, Kaposi [3] has described two examples of "sarco-carinomatous" tumours of the face of girls, aged respectively ten and seven years, who had suffered from earliest infancy with xeroderma of the part; and Lapointe and Lecéne [4] the same type of disease in the right adrenal of an infant nineteen months old etc.

Maier [5] has described a thyroid tumour from a woman aged forty, in

[1] "Die krankhaften Geschwülste," 1863.

[2] My book on "Diseases of the Breast," p. 170.

[3] Hebra's "Skin Diseases," Sydenham Society's Translation, vol. iii., p. 254; and vol. iv., p. 222.

[4] *Bull. et Mém. Soc. Anat.*, Paris, November, 1904.

[5] *Arch. f. path. Anat.*, 1877, Bd. lxx., S. 378.

which ossifying and chondrifying sarcoma and carcinoma were combined ; and other instances of thyroid sarco-carcinoma have been reported by Donati, Syme, Schmorl, Kaufmann, etc. ; while Wells,[1] Loeb, and Kummer [2] have likewise met with this combination in thyroid tumours of dogs.

It is, however, in the uterus that the most numerous and best studied examples of this kind of morbid growth have been found.

Some of the cases to be cited in this connexion have been adversely criticized ; but, in my opinion, their validity has not been impaired.

I have previously referred to the remarkable cases of Niebergall and Milford, in which two different forms of malignant disease were present in the same uterus, together with various non-malignant growths.

Then there is Montgomery's case, in which glandular epithelioma of the cervix was concomitant with sarcoma of the corpus.

In Keller's [3] case, a round and spindle-celled polypoid sarcoma of the cervix was associated with glandular epithelioma of the same part.

Emanuel [4] found a round-celled, polypoid sarcomatous tumour, growing from the wall of the corpus, concurrently with diffuse glandular epithelioma of the mucosa of the same part.

In Abel and Landau's [5] case, glandular epithelioma of the cervix was associated with diffuse sarcoma of the uterine mucosa.

In Rabl-Rückhardt's [6] patient, after a polypoid, sarcomatous tumour had been spontaneously expelled from the uterus, the mucosa was then found to be affected with diffuse glandular cancer. At several points, cancerous glandular ingrowths from the overlying diseased mucosa, had penetrated into the sarcomatous tumour.

Franqué's [7] three cases may next be cited : in the first of these, round- and myeloid-celled sarcoma of the mucosa of the corpus, was concurrent with glandular epithelioma of the cervix ; in the second, cylinder-celled glandular epithelioma of the corpus was present, together with round-celled sarcoma of the adjacent part of the cervix, the two morbid growths being quite distinct, though contiguous ; and, in the third, sarcoma of the uterine wall was concomitant with glandular epithelioma of the cervix.

Finally, mention may be made of H. Spencer's [8] case, in which glandular epithelioma of the corpus, was concurrent with small round-celled sarcoma of the same locality.

Similar series of cases have been reported in connexion with the ovary.

It requires no great stretch of the imagination to see how, from the fusion of closely contiguous growths of different kinds, such as the foregoing series reveals, true mixed tumours may result, of which an example has been reported by Rosenstein [9] in the uterus ; and, in other parts of the body, by Fletcher,[10] Maier,[11] Kuhnart [12] and others.

[1] *Journal of Pathology and Bacteriology*, 1901, vol. vii., p. 352.
[2] *Rev. Méd. de la Suisse Romande*, 1898, t. viii., p. 703.
[3] *Zeits. f. Geb. u. Gyn.*, 1890, Bd. xx., S. 116. [4] *Ibid.*, 1896, Bd. xxxiv., S. 1.
[5] *Arch. f. Gyn.*, Bd. xxxii., xxxiv., and xxxv.
[6] *Beitr. z. Geb. u. Gyn.*, 1872, Bd. l., S. 76.
[7] *Zeits. f. Geb. u. Gyn.*, 1899, Bd. xl., S. 183.
[8] Transactions of the Pathological Society, 1906 ; also *Lancet*, 1905, vol. ii., p. 1109.
[9] *Arch. f. path. Anat.*, 1883, Bd. xcii., S. 191.
[10] Transactions of the Pathological Society, London, 1902, vol. lii., p. 199.
[11] *Arch. f. path. Anat.*, Bd. lxx., S. 378. [12] *Arch. f. Gyn.*, 1874, Bd. vi.

Although the histological and some of the general biological characters—especially the reproduction of the original mixed type in the disseminative lesions of certain rare malignant growths—seem to countenance the belief in the existence of mixed malignant tumours, it must not be concluded on this account, that transitions from one type of malignant growth to another occur (transformation, metaplasia). Never have transitions of this kind been verified. This proposition rests on a mistaken apprehension as to the origin of the tissue cells, the specificity of which modern cytological studies have revealed.

Thus, among neoplastic tissues, as among the normal tissues, there are no transitions from one specific type to another; in fact, the metaplasia of Virchow has no real existence.

### The Association of Malignant with Non-malignant Tumours.

It not uncommonly happens that malignant and non-malignant tumours are associated, in the same individual, of which some remarkable examples have been cited above.

In further illustration of the subject, reference may be made to the case of a woman, aged fifty-two, who died after abdominal hysterectomy for uterine myomata, when Lubarsch [1] found sarcoma of the gall-bladder, a large adenoid polypus of the stomach, a small "tumour" in the spleen, lipoma of the right kidney, "struma suprarenalis aberrans," cystic kidneys and enchondroma of the right pleura.

In Guy's Hospital Museum [2] is a specimen of cancer of the uterus, concomitant with adenoma of the right adrenal; and Bosanquet [3] has found cancer of the stomach, with adenoma of both adrenals.[4]

Lubarsch [5] has met with cancer of the stomach, in association with multiple polypi and cystic adenoma of the part; and, many instances of this kind have been reported, in the large intestine. Maier [6] encountered enchondroma of the kidney, with cancer of the same; and, enchondroma of the subcutaneous tissue of the thorax, also with cancer.

De Santi [7] found fibroma papillare of the nasal septum, with rodent ulcer of the nose.

Milian [8] epithelioma of the lung and cancer of the parotid, with adenomata of the liver.

Many instances of the association of cancer of the liver with "adenoma" of the same, have also been reported (Schmieden,[9] Wells,[10] Eggel [11] etc.); and in the thyroid this concomitancy is far from uncommon.

[1] Cited by Walter (*Arch. f. klin. Chir.*, 1896, Bd. liii., S. 1).
[2] No. 2,020, Pathological catalogue.
[3] Transactions of the Pathological Society, London, 1902, vol. lii., p. 64.
[4] For other instances of concomitant adrenal tumours and cancer elsewhere, *vide* Chapter IX.
[5] Cited by Walter.
[6] *Arch. f. path. Anat.* 1877, Bd. lxx., S. 378.
[7] *Lancet*, December 8, 1894.
[8] *Bull. et Mém. Soc. Anat.*, Paris, March 19, 1897.
[9] *Arch. f. path. Anat.*, 1900, Bd. clix., S. 290.
[10] *American Journal of Medical Science*, 1903, p. 403.
[11] *Ziegler's Beitr. z. path. Anat.*, etc., 1901, Bd. xxx., S. 506.

Smyly[1] found spindle-celled sarcoma of the lower end of the femur, concomitant with a large ossified enchondroma, and a lipoma, all of the same vicinity.

Uterine myomata are often present in the cancerous as in the non-cancerous; thus, of 79 necropsies for uterine cancer in my list, myomata were present in 5 or in 6·3 per cent., and in many cases mucosal polypi as well. 11·3 per cent. of my breast cancer cases, were subject to uterine myomata. As mentioned in the preceding chapter, in cancer of other localities, uterine myomata coexisted in 18·5 per cent. of the necropsies.

Tate[2] has seen cylinder-celled epithelioma of the corpus uteri concomitant with myomata of the same, and with myoma of the left ovary; Cullen[3] found cancer of the corpus uteri, with multiple uterine myomata, and papillary cystoma of both ovaries.

According to Chiari,[4] the subjects of uterine myoma are unduly prone to cancer. Of 25 women with myomata under his observation, 2 had cancer of the uterus, 1 cancer of the breast, and 6 had cancer of other organs. This is a very slender basis on which to rest such a sweeping statement. If Chiari's views were correct, we should expect to find uterine myomata much more frequently in the cancerous than in the non-cancerous. But, of 159 female cancer necropsies in my list, uterine myomata were present in only 20, or in 12·5 per cent.; whereas, according to Bayle, they are found in 20 per cent. of all women over thirty-five. Hence Chiari's conclusion must be rejected.

In like manner ovarian cystomata—oöphoronic, parovarian and dermoid—are fairly often found in association with malignant tumours: thus, of Lebert's 45 uterine cancer necropsies, ovarian cystomata were present in 3; and, of Winckel's numerous cases of ovarian cystomata, 8 per cent. had also uterine cancer.

Of 44 necropsies for mammary cancer in my list, ovarian cystomata were present in 3.

The association of ovarian cystomata with malignant disease of other parts of the body, especially of the gastro-intestinal tract, is also an occurrence of no great rarity.[5]

Of 85 female mammary cancer patients in my list, fatty tumours were present in 2; one of these patients was also the subject of multiple molluscum fibrosum, an ovarian dermoid, and a mucous polypus of the cervix uteri.

De Morgan and Murchison have each seen uterine cancer, associated with multiple lipomata of various parts of the body.

[1] Transactions of the International Medical Congress, London, 1881, vol. i., p. 114 (specimen exhibited in museum).

[2] Transactions of the Obstetrical Society, London, 1905, vol. xlvi., p. 138.

[3] "Cancer of the Uterus," 1901, p. 463.

[4] "Klin. der Geburts.," etc. Erlangen, 1853.

[5] Lockyer (*Practitioner*, November, 1903), case of cancer of rectum with ovarian cystomata; and Terrier (*Union Méd.*, Paris, 1887, t. xliv., p. 5), sarcoma of transverse colon, with cystoma of right ovary. Deanesly (*British Medical Journal*, 1902, vol. i., p. 1148) and Boucher (*New York Medical Record*, 1902, November 22, p. 816), cases of cancer of colon, with bilateral ovarian cystoma, etc.

## CHAPTER XIV

# THE INFLUENCE OF SEX

THE influence of sex in determining the localization and incidence of tumours is very great; and, it is noteworthy, that both malignant and non-malignant varieties are subject thereto. This seems to imply, that the conditions determining the growth of both varieties of tumours are the same in kind, and differ only in degree.

In illustration of the subject, reference may be made to my analysis of 15,481 primary tumours of all kinds, consecutively under treatment at four large metropolitan hospitals, during a period of from sixteen to twenty-one years, as follows :—

TABLE SHOWING THE SEX INCIDENCE OF 15,481 PRIMARY TUMOURS.

| | Total. | Males. | Females. | Sex Ratio. |
|---|---|---|---|---|
| Epithelioma—*i.e.*, malignant epithelial tumours .. .. .. .. .. | 7878 | 2861 | 5017 | 1 to 1·75 |
| Sarcoma .. .. .. .. .. | 1350 | 702 | 648 | 1 „ 0·92 |
| Non-malignant tumours .. .. .. | 4613 | 1179 | 3434 | 1 „ 2·91 |
| Cysts .. .. .. .. .. | 1640 | 449 | 1191 | 1 „ 2·65 |
| | 15,481 | 5,191 | 10,290 | 1 „ 1·98 |

The greater prevalence of malignant epithelial tumours among females, is entirely due to the frequency with which the mammæ and uterus are affected, the corresponding structures in males very rarely originating the disease [1]; while, in nearly every other locality, the male liability preponderates, as I have elsewhere pointed out.[2]

Hence sarcomatous tumours, which do not manifest this special proclivity to attack the female reproductive organs, are more equally distributed between the sexes.

My analysis also shows, that the relative proneness of females to non-malignant tumours and cysts, is even greater than it is to malignant epithelial tumours; and, as a detailed examination of the matter indicates, this is attributable to the undue frequency with which in women the uterus and ovaries are attacked, the corresponding male organs seldom being affected by tumours of this type.

An inference from the foregoing is, that we must seek for an explana-

[1] The national mortality returns, for 1900, show that the female cancer death-rate—less the mortality due to cancer of the mammary and generative organs—was 583 per million, as against 660, the corresponding male rate.

[2] Chapter XVII.

tion of these remarkable diversities in morbid proclivity, in biological peculiarities inherent to the affected parts, and in their concomitant developmental and structural diversities—all of which are ultimately ascribable to functional modifications—rather than to any general constitutional condition correlated with sex. As mentioned in a previous chapter, the greater proclivity of human females to cancer, than the females of animals, is due rather to circumstances connected with the special sheltered environment of the former, than to any peculiarity connected directly with sex. It accords with this that of late—when owing to urbanization the conditions of existence for men and women have been rendered less divergent—the disparity in cancer proclivity has lessened, and this change is still in progress. Of like import is the great frequency of cancer in castrated animals of both sexes, to which I have previously referred.[1]

We may also turn for information as to the influence of sex in malignant disease, to the national mortality returns.

Thus, the Sixty-third Report of the Registrar-General, for the year 1900, shows that among males the cancer mortality was 672 per million living of that sex, the corresponding figure for females being 975 : in the same year 26,721 persons died of the disease, of whom 10,475 were males and 16,246 females—the sex ratio being 1 male to 1·5 females ; 1 male died of cancer to every 29 male deaths from all causes, and 1 female died of this disease to every 17 female deaths ; and finally, of persons aged thirty-five years and upwards, 1 in 15 men and 1 in 9 women died of cancer.

For the year 1906, the respective cancer death-rates were 794 per million for males, and 1,032 for females, the sex ratio being 1 male to 1·3 females.

As I have elsewhere shown,[2] this increasing cancer mortality has affected males, to a much greater extent than females. In further illustration of this subject, the foregoing data may be compared with those derived from the massed national mortality returns for the twenty-five years 1848-1872, which show a sex ratio of 1 male to 2·29 females ; 1 male having died of cancer to every 100 male deaths, and 1 female to every 41 female deaths.

It seems likely, if the disproportionate increase of cancer among males, now going on in our country, continues unchecked, that the disease will eventually become more prevalent among men than among women, as is already the case in Australia and New Zealand ; thus, in 1900, the cancer death-rate for all Australia was 591 for males, as against only 550 for females, and this excess of male cancer mortality has been apparent ever since 1870.

In the United States, and in such European countries as publish national mortality returns, the sex incidence—in its main features—is similar to that of our country. Thus, of 29,475 cancer deaths in the United States, during 1900, 11,436 were males and 18,039 females, the sex ratio being 1 to 1·5.

From these data it may be concluded that, while the female liability

[1] Chapter V. and VII.

[2] Chapter III.

to cancer in nearly all modern communities, still much exceeds the liability of males; yet, this disparity in sex incidence, is tending rapidly to disappear. As I have previously mentioned, this may be accounted for as the result of the changed conditions of modern life which predispose to cancer, pressing with disproportionate severity on men.

The information derivable from crude national mortality returns is valuable, chiefly on account of the *massif* of the totals, which tend to mitigate the disturbing influence of the many defects inherent to such compilations. It is, however, easier to point out flaws of this kind, than to remedy them; for, with almost every "correction," new sources of error are necessarily introduced, so that the indications furnished by the crude returns are often more reliable, as resting on a broader basis, than those furnished by "corrected" data.

Modern statisticians sometimes forget, that compilations of this kind are necessarily unsuited by their very nature for the discrimination of fine details; it is rather for furnishing reliable general indications, that these monumental works are so valuable.

In drawing conclusions as to the relative frequency of cancer in the two sexes, from the crude mortality sex ratios, it is evident that allowance should be made for the fact, that in most of the countries concerned, the sexes are unequally represented in the general population, females preponderating. This, of course, tends to minimize the disparity revealed by the crude ratios; although the disturbing factor in this case is not sufficiently potent, to change the character of the general result.

Even by comparing the respective cancer death-rates of males and females, we are unable exactly to discriminate the relative liability of the sexes; because, the frequency of cancer varies at different ages, and the age distribution of an equal number of both sexes is also very different, women living to a greater age than men etc.

As a corrective to disturbing influences of this kind, the cancer mortality may be calculated separately for those of each sex above a certain age, say thirty-five years old and upwards, of which I have previously given the results for our country.

But even such a comparatively perfect method as this, fails to quite satisfy some statistical experts. Laspeyres [1] proposes to solve the problem by calculating separately the mortality of each sex, at each of the various age-periods, insisting that the mortality of each sex varies greatly according to age: thus, during the age-period thirty to fifty years, he finds that the cancer mortality of women is much greater than that of men; [2] while, from fifty to seventy and upwards, the male mortality is the greater. De Bovis [3] proposes to attain the same end, by placing side by side 100,000 of each sex, arranged according to their respective age distribution; and then calculating *by age*, the number of cancer deaths that each of these totals will produce. These results being derived from male and female populations ide tical in their number and composition, readily furnish the required sex ratios, when the corresponding numbers are compared.

[1] *Cent. f. allg. Gesundheitspflege*, 1901, S. 342.
[2] This result is mainly due to the precocity of uterine and mammary cancer.
[3] *La Semaine Méd.*, No. 37, 1902.

Applying this method to our population, aged twenty-five and upwards, he finds that the relative liability of the sexes to cancer is 100 males to 139 females ; in Holland, the corresponding ratio is 100 to 123 ; in Prussia, 100 to 101 ; while for Norway, it is 100 males to 87 females ; and in Switzerland, 100 to 88.

The *localization* of malignant and other tumours is also much influenced by sex, as is well illustrated by the tabular statements given in another chapter.[1] As the national mortality returns show, in 70·6 per cent. of the cancer deaths among males, the disease is situated in the alimentary system (stomach 21·4) ; among females, the corresponding percentage is 43·3 (stomach 13·2). Uterine (23·5) and mammary (15·8) forms of the malady, account for 39·3 per cent. of the total female cancer mortality.

The hospital returns analysed by me show, that 68·6 per cent. of all malignant epithelial tumours, among males, were located in the alimentary system, the corresponding percentage for females being 15·2 : among females, 74·3 per cent. of these tumours were situated in the breast (40·3) and uterus (34).

No such striking sex diversities in localization are noticeable among the sarcomata, as the figures in my analysis show ; and of 1,789 sarcomata tabulated in the national mortality returns (1903), 860 were in females and 929 in males.

The following data by Dr. Tatham, which are based on the national mortality returns for 1897-1900 (comprising in all 102,685 deaths from cancer), further illustrate this subject.

TABLE SHOWING THE SEX INCIDENCE OF CANCER IN RELATION TO LOCALIZATION.

| Localization. | Deaths. | | Death-rates per Million Living. | |
|---|---|---|---|---|
| | Males. | Females. | Males. | Females. |
| Uterus, mamma, and reproductive organs .. .. | 726 | 25,151 | 12 | 384 |
| Stomach .. .. .. | 8369 | 8355 | 136 | 127 |
| Intestine .. .. .. | 6312 | 6731 | 103 | 103 |
| Liver .. .. .. | 5532 | 8654 | 90 | 132 |
| Œsophagus .. .. .. | 2358 | 852 | 38 | 13 |
| Tongue .. .. .. | 2124 | 271 | 35 | 4 |
| Throat .. .. .. | 891 | 334 | 15 | 5 |
| Lip .. .. .. .. | 647 | 74 | 11 | 1 |
| Mouth .. .. .. | 508 | 115 | 8 | 2 |
| All parts .. .. .. | 40,317 | 62,368 | 657 | 952 |

The *age incidence* of cancer is considerably earlier in women than in men, owing to the precocity of the uterine, mammary and ovarian forms of the disease ; thus, according to Karl Pearson, the mean age of 2,368 female cancer patients was 48·8 years, as against 53·3 years for 632 male patients. Pearson also finds that the age incidence of cancer in man, is more variable than in women.

[1] Chapter XVIII.

I have found the mean age, at *onset*, of the chief local forms of malignant epithelial tumours, to be as follows :—for *females*, uterus 44, mamma 48, stomach 47·4, rectum 50·5, skin 50, œsophagus 50·6, tongue and mouth 50, rodent ulcer 42·5 etc. ; and for *males*, stomach 51·1, tongue and mouth 53·8, lower lip 52·4, rectum 49·7, œsophagus 56, skin 52·4, mamma 50, rodent ulcer 48·8 etc.[1]

The following tabular statement from the Registrar-General's Reports, indicates the mean annual mortality from cancer per million living of each sex, at successive age-periods, during the decennia 1851-1860 and 1891-1900 respectively.

TABLE SHOWING THE CANCER DEATH-RATES OF EACH SEX, AT SUCCESSIVE AGE-PERIODS, DURING THE DECENNIA 1851-1860 AND 1891-1900.

| AGE-PERIODS. | MALES. | | FEMALES. | |
|---|---|---|---|---|
| | 1851-1860. | 1891-1900. | 1851-1860. | 1891-1900. |
| All ages .. .. .. | 195 | 600 | 434 | 906 |
| Under 5 years .. .. | 21 | 33 | 23 | 28 |
| 5 to 10 .. .. .. | 10 | 18 | 9 | 14 |
| 10 „ 15 .. .. .. | 8 | 19 | 9 | 14 |
| 15 „ 20 .. .. .. | 16 | 32 | 18 | 27 |
| 20 „ 25 .. .. .. | 27 | 51 | 30 | 39 |
| 25 „ 35 .. .. .. | 63 | 99 | 141 | 175 |
| 35 „ 45 .. .. .. | 174 | 384 | 592 | 891 |
| 45 „ 55 .. .. .. | 422 | 1300 | 1278 | 2323 |
| 55 „ 65 .. .. .. | 931 | 3160 | 1853 | 4099 |
| 65 „ 75 .. .. .. | 1504 | 5325 | 2350 | 5829 |
| Over 75 .. .. .. | 1749 | 5824 | 2341 | 6377 |

These data clearly indicate the very much higher mortality of females, than of males, at all age-periods after the twenty-fifth year ; and they also show the rapid rise of mortality for both sexes, in the age-periods succeeding the twenty-fifth year. It is noteworthy in this connexion, that the female mortality shows much greater augmentation than the male mortality, both in the aggregate, and at each successive age-period after the twenty-fifth year. The influence of sex in relation to age incidence is, indeed, most marked between the twenty-fifth and fifty-fifth years.

In infancy, childhood and early life, prior to the twenty-fifth year, there is no such marked difference in morbid proclivity ; for, most of the tumours of this early period being sarcomatous, the sex incidence is approximately equal, with however a distinct bias in favour of males.

[1] According to Lebert ("Traité des mal. cancéruses," 1851), the average age at onset of the chief forms of cancer then was as follows : uterus 44, tongue 47, mamma 50, stomach 54, bladder 55, intestine 55, skin 57, liver 57, and œsophagus 60 years : the mean age for all cancer, he estimated at about 51 years. Sibley (Transactions of the Med.-Chir. Society, London, 1859, vol. xlii.) gives 43·38 as the average age of uterine-cancer patients ; 48·6 for mammary, and 55·3 for lip cancer in males. Nunn ("Cancer of the Breast," 1882) estimates the average age of uterine cancer at 45·7, and of mammary at 50·4. From these figures it may be inferred that there has been no marked alteration in the age incidence of cancer during the last half-century.

## CHAPTER XV

### THE INFLUENCE OF AGE

In order to appreciate the influence of age in the ætiology of malignant tumours—the great importance of which I have strongly insisted on in all my publications [1]—it is necessary to be accurately acquainted with the actual facts as to the age distribution of this particular malady; and also to have some knowledge as to the *rôle* of age, with regard to mortality in general.

The best source of information as to the incidence of malignant disease in general, at the various age-periods, is to be found in the national mortality returns. The subjoined table, from the Sixty-third Report of the Registrar-General, shows the age distribution of the deaths from this cause in England and Wales, during the year 1900, as follows :—

TABLE I.

SHOWING THE AGE DISTRIBUTION OF CANCER MORTALITY IN EACH SEX DURING 1900.

| | Under 5 Years. | 5- | 10- | 15- | 20- | 25- | 35- | 45- | 55- | 65- | 75- | 85 and upwards. | All Ages. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Males .. | 61 | 21 | 36 | 47 | 83 | 235 | 748 | 1942 | 3245 | 2832 | 1095 | 110 | 10,475 |
| Females .. | 58 | 38 | 32 | 53 | 73 | 502 | 1803 | 3539 | 4509 | 3799 | 1641 | 199 | 16,246 |

From these data we learn the absolute frequency of the mortality at the various age-periods, the maximum being attained for both sexes, during the decennium fifty-five to sixty-five. It will be noted that 95 per cent. of the total deaths occur after the thirty-fifth year, and 86 per cent. after the forty-fifth year.[2] These data tell us very little as to the relative tendency of each sex to cancer, at different periods. In order to ascertain this, we must compare the figures with the total number of each sex living, at the corresponding age-periods. The following table, which has been compiled on this basis, shows the mean cancer mortality, per million living of each sex, in groups of ages, for the year 1900.

[1] "Twentieth Century Practice of Medicine," 1898, vol. xvii., pp. 241, 487; "Diseases of the Breast, with Special Reference to Cancer," 1894, p. 238; "Uterine Tumours," 1901, p. 242; and "The Principles of Cancer and Tumour Formation," 1888.

[2] In marked contrast with the above, 76 per cent. of all deaths from phthisis occur prior to the forty-fifth year.

## TABLE II.

SHOWING THE CANCER DEATH-RATES IN EACH SEX, AT DIFFERENT AGE-PERIODS, FOR 1900.

| | Under 5 Years. | 5- | 10- | 15- | 20- | 25- | 35- | 45- | 55- | 65- | 75 and upwards | All Ages. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Males .. | 31 | 11 | 20 | 29 | 60 | 101 | 418 | 1483 | 3796 | 5735 | 6715 | 672 |
| Females .. | 29 | 20 | 18 | 32 | 47 | 197 | 942 | 2433 | 4561 | 6254 | 7468 | 975 |

From these sources, as well as from the data given at the end of the preceding chapter, we learn that cancer begins to be frequent—in both sexes—after the twenty-fifth year; and that the relative mortality from it increases rapidly and progressively, with each successive decade, until the seventy-fifth year, females being in this respect much more precocious than males from the start, as is specially noticeable in the age-period forty-five to fifty-five.

Dr. Bashford[1] regards this progressive age distribution as "specially characteristic" of cancer, but this is a mistake; for, a similar tendency is noticeable with regard to mortality from most diseases, *e.g.*, diseases of the urinary, respiratory and nervous systems, diabetes etc. Indeed, the liability of the cancer mortality to increase with age, as compared with the corresponding liability to death generally, shows undue rapidity of augmentation up to the decennium forty-five to fifty-five; but, after this period, the general mortality increases far more rapidly than the cancer mortality. Referring to this subject, Dr. Ogle remarks[2]: "In simply saying that the liability to death from cancer increases with age, no more is said than may be stated with equal truth of liability to death generally. The question is, Does the annual liability to death from cancer increase more rapidly than the annual liability to death of all kinds?" To answer this query, he has compiled the following table, showing the ratio of total deaths from cancer during the decennium 1871-1880, at successive age-periods.

## TABLE III.

SHOWING THE TOTAL DEATHS TO ONE FROM CANCER AT SUCCESSIVE AGE-PERIODS

| Age-Periods. | Persons. | Males. | Females. |
|---|---|---|---|
| 20 to 25 years .. .. .. .. .. | 255 | 262 | 248 |
| 25 „ 35 „ .. .. .. .. .. | 71 | 131 | 49 |
| 35 „ 45 „ .. .. .. .. .. | 24 | 57 | 15 |
| 45 „ 55 „ .. .. .. .. .. | 14 | 28 | 9 |
| 55 „ 65 „ .. .. .. .. .. | 14 | 22 | 10 |
| 65 „ 75 „ .. .. .. .. .. | 21 | 27 | 17 |
| 75 and upwards .. .. .. .. .. | 48 | 56 | 44 |

[1] Scientific Report of the Imperial Cancer Research Fund, 1905, No. 2, pt. 1.
[2] Forty-seventh Annual Report of the Registrar-General for England and Wales.

As will be gathered from the above, the characteristic feature of the cancer mortality is, *not* its progressive increase with advance of years—for this it shares with most other lethal maladies—but its disproportionate augmentation in the post-meridian periods—*i.e.*, forty-five to sixty-five.

The above table also shows well, the relative liability of the sexes at different ages. It will be noticed that the proclivity of females increases until the decennium forty-five to fifty-five, when it attains its maximum, after which it lessens progressively at each decade in a marked degree: on the other hand, the male maximum is not attained until a later period, viz., the decennium fifty-five to sixty-five, corresponding with the slower decline of reproductive activity in the male sex.

With regard to cancer of the female breast, statistics compiled on this principle by Paget [1] and Nunn,[2] show that the period of its greatest relative frequency is between the fortieth and fiftieth years. Nunn's table, which was compiled for him by an actuary, is as follows:—

## TABLE IV.

SHOWING THE RELATIVE FREQUENCY OF MAMMARY CANCER AT THE DIFFERENT AGE-PERIODS.

| Age-Periods. | Per Cent. |
|---|---|
| 25 to 30 years | ·831 |
| 30 „ 35 „ | 3·933 |
| 35 „ 40 „ | 8·783 |
| 40 „ 45 „ | 12·311 |
| 45 „ 50 „ | 18·006 |
| 50 „ 55 „ | 16·161 |
| 55 „ 60 „ | 8·368 |
| 60 „ 65 „ | 9·696 |
| 65 „ 70 „ | 9·181 |
| 70 „ 75 „ | 4·983 |
| 75 „ 80 „ | 3·923 |
| 80 „ 85 „ | 3·824 |
| | 100·000 |

This shows that the relative liability of women to mammary cancer lessens progressively, in a marked degree, at each age-period after fifty-five.

Considerations of this kind induced me to investigate the mortality from cancer of centenarians, and of aged persons of eighty years upwards. The information thus obtained shows, that these aged persons are relatively much less prone to the disease than their juniors. Cancer seldom originates in extreme old age. Thus, of 1,087 centenarians, of whom the causes of death are tabulated in the Registrar-General's Reports for the fifteen years 1871-1885, only 5 died of cancer, or 1 in 217; of the 295 males, 2 died of cancer, or 1 in 147; and of the 792 females, 3 died of it, or 1 in 264.

The localization of the disease in these centenarians is stated in only one case, this patient being a woman, who died aged 106, of "cancer of the eye and wrist."

[1] "Lectures on Surgical Pathology," 1853, vol. ii., p. 326.
[2] "Cancer of the Breast," 1882, p. 161.

Humphry's report [1] on the maladies of old people, is of similar import. Thus, among 202 persons (males 92, females 110), ninety years of age and upwards, there was not a single instance of malignant disease; and, of 622 persons (males 340, females 282), between eighty and ninety years old, there were only 14 instances of it. Thus, of these 824 aged persons, malignant disease was met with only in 1·7 per cent. of the total cases, or in the ratio of 1 to 58·8. Of 432 males, 7 were cancerous, or 1 in 61·7; and of 392 females, 7 were similarly affected, or 1 in 56. Of the males, the lip was the seat of the disease in 3 cases; the penis, ear, finger and shoulder, each in 1 case. Of the females, in 5 the mamma was the part affected, and in 2 the face.

These facts clearly show that cancer is *not* a senile disease; and that senility, *per se*, plays no part in its development.

The contrary belief, which has lately been advocated in influential quarters, is the outcome of misunderstanding of the facts; and especially of failure to appreciate "age incidence," in respect to mortality in general, as I have above indicated.

Thus, the special feature in the age incidence of malignant disease is, its connexion with decline in reproductive activity; and not in its fancied relation to senility.

In animals, as in mankind, the maximum incidence of cancer likewise coincides with decline in reproductive activity, rather than with senility *per se*, as I have previously had occasion to indicate.[2]

In the preceding chapter, some reference was made to the influence of sex, in respect to the localization of malignant tumours.

In further elucidation of this subject, I now submit the subjoined table, showing the absolute frequency of the malady in the chief sites, at different age-periods, in each sex, the data being derived from the national mortality reports for the three years 1901-1903 (see Table V., p. 321).

From these figures the corresponding death-rates may be calculated, by employing the usual formula.[3]

It should be borne in mind that the figures refer to the age incidence at death; and not to the first obvious manifestation of the disease. Even so, however, they clearly indicate the precocity of the uterine, ovarian, and mammary forms of the disease in women: in both sexes, gastric, hepatic and rectal cancers occupy an intermediate position in respect to age incidence; while, lingual, intestinal, œsophageal and cutaneous manifestations are of late occurrence, in both sexes.

Hospital mortality statistics give similar results.

For some of the chief local manifestations of malignant epithelial tumours, I have compiled the following data, showing the age at the *onset* of the first obvious symptoms of the disease, among hospital patients (see Table VI., p. 322).

The general import of these data is to diminish the sharpness of the diversities in age incidence, revealed by the mortality returns; which are thus seen to be due, to a considerable extent, to differences in the duration of life of the various local forms of the disease. In estimating

[1] *British Medical Journal*, July 30, 1887. [2] Chapter V.
[3] For details, *vide* Sixty-sixth Annual Report of the Registrar-General for 1903.

the influence of age, in this connexion, it is necessary not to lose sight of this important consideration.

A curious feature revealed by careful study of age incidence, in relation to uterine malignant epithelial growths is, that this malady originates in the corpus, at a much later period than in the cervix.

## TABLE V.

SHOWING THE AGE AND SEX INCIDENCE OF MALIGNANT TUMOURS IN RESPECT TO LOCALIZATION, BASED ON THE NATIONAL MORTALITY RETURNS 1901-1903.

| Localization. | Under 25 Years. | 25- | 35- | 45- | 55- | 65- | 75- | 85 and upwards. | Total. |
|---|---|---|---|---|---|---|---|---|---|
| MALES. | | | | | | | | | |
| Stomach .. | 13 | 116 | 527 | 1374 | 2390 | 2168 | 728 | 33 | 7349 |
| Liver and gall-bladder .. | 42 | 61 | 287 | 817 | 1471 | 1362 | 511 | 45 | 4596 |
| Rectum .. | 26 | 86 | 210 | 614 | 1060 | 918 | 404 | 32 | 3350 |
| Tongue and mouth .. | 9 | 17 | 176 | 593 | 844 | 618 | 225 | 20 | 2501 |
| Intestines .. | 22 | 64 | 169 | 412 | 711 | 723 | 267 | 17 | 2385 |
| Œsophagus .. | 1 | 8 | 125 | 504 | 752 | 524 | 185 | 8 | 2107 |
| Skin .. | 15 | 20 | 58 | 155 | 280 | 408 | 365 | 89 | 1390 |
| Bladder and urethra .. | 9 | 10 | 45 | 164 | 273 | 379 | 171 | 17 | 1068 |
| Jaw .. | 28 | 9 | 71 | 215 | 314 | 267 | 107 | 1 | 1012 |
| All other sites | 539 | 367 | 760 | 1580 | 2179 | 1860 | 681 | 64 | 8030 |
| Totals | 704 | 758 | 2428 | 6427 | 10,274 | 9227 | 3644 | 326 | 33,788 |
| FEMALES. | | | | | | | | | |
| Uterus .. | 20 | 518 | 2094 | 3472 | 3061 | 1861 | 620 | 68 | 11,714 |
| Mamma .. | 4 | 179 | 1040 | 2112 | 2209 | 1682 | 952 | 189 | 8367 |
| Stomach .. | 7 | 107 | 503 | 1289 | 2135 | 2167 | 839 | 72 | 7119 |
| Liver and gall-bladder .. | 32 | 77 | 418 | 1173 | 2168 | 2111 | 882 | 74 | 6935 |
| Intestines .. | 19 | 71 | 227 | 584 | 945 | 1005 | 444 | 43 | 3338 |
| Rectum .. | 17 | 100 | 236 | 553 | 834 | 793 | 372 | 34 | 2939 |
| Ovary .. | 30 | 72 | 168 | 276 | 222 | 126 | 24 | 2 | 920 |
| Abdomen .. | 20 | 17 | 47 | 179 | 235 | 269 | 108 | 13 | 888 |
| Peritoneum .. | 10 | 28 | 74 | 147 | 273 | 223 | 76 | 9 | 840 |
| Œsophagus .. | 1 | 37 | 79 | 140 | 164 | 207 | 92 | 5 | 725 |
| Skin .. | 6 | 10 | 32 | 67 | 110 | 173 | 189 | 50 | 637 |
| Tongue and mouth .. | 6 | 22 | 31 | 48 | 83 | 122 | 54 | 4 | 370 |
| All other sites | 422 | 266 | 630 | 1093 | 1410 | 1323 | 616 | 108 | 5868 |
| Totals .. | 594 | 1504 | 5579 | 11,133 | 13,849 | 12,062 | 5268 | 671 | 50,660 |

According to Hofmeier, the average age of patients thus affected at the onset of the disease is 54·5 years, or over ten years later than the age at which cancer of the cervix supervenes.

As the subjoined analysis of the age incidence shows, most cases of this local variety of the disease, arise during the decennium fifty to sixty

(51 per cent.); whereas, with epithelioma of the cervix, the period of maximum frequency is the decennium thirty-five to forty-five (37 per cent.).

In illustration of this, I have made the following analysis showing the age incidence of epithelioma of the corpus uteri, in 100 cases reported by Pichot, Gusserow, J. Williams and myself, as follows:—twenty to thirty years, in 8·3 cases; thirty to forty, in 3·6; forty to fifty, in 19; fifty to sixty, in 51·2; sixty to seventy, in 16·7; and, at over seventy years, in 1·2 cases.

Although many pathologists even now regard the sarcomata as a form of malignant disease, chiefly met with in quite young persons, yet,

## TABLE VI.

SHOWING THE AGE AND SEX INCIDENCE OF EPITHELIOMA IN RESPECT TO LOCALIZATION, BASED ON THE AGE AT ONSET.

| Localization. | Under 25 Years. | 25- | 35- | 45- | 55- | 65- | 75 and upwards. | Total. | Aver. | Max. | Min. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Males.** | | | | | | | | | | | |
| Stomach .. | 2 | 4 | 9 | 20 | 16 | 7 | 1 | 59 | 51·1 | 76 | 19·25 |
| Tongue and mouth .. | — | 1 | 19 | 38 | 32 | 9 | 1 | 100 | 53·8 | 78·5 | 25·6 |
| Lower lip .. | — | 8 | 17 | 34 | 27 | 13 | 1 | 100 | 52·4 | 75·5 | 26 |
| Rectum .. | 4 | 8 | 18 | 22 | 20 | 11 | — | 83 | 49·7 | 74 | 16·75 |
| Mamma .. | 2 | 11 | 23 | 32 | 19 | 12 | 1 | 100 | 50 | 82 | 20 |
| Skin .. | — | 7 | 13 | 19 | 19 | 7 | 3 | 68 | 52·4 | 85·25 | 27 |
| "Rodent ulcer" | — | 4 | 5 | 4 | 7 | 2 | — | 22 | 48·5 | 70 | 26 |
| **Females.** | | | | | | | | | | | |
| Uterus (cervix) | 0·2 | 18 | 37 | 29 | 14 | 1 | 0·8 | % on 500 | 44 | 83 | 22·25 |
| Mamma .. | 0·6 | 10 | 30 | 35 | 19 | 4·4 | 1 | % on 500 | 48 | 84 | 24 |
| Rectum .. | 3 | 9 | 9 | 15 | 23 | 6 | 1 | 66 | 50·4 | 88 | 21·8 |
| Tongue and mouth .. | 3 | 12 | 14 | 39 | 19 | 12 | 1 | % on 90 | 50 | 77·5 | 24 |
| Stomach .. | — | 5 | 11 | 10 | 7 | 2 | 1 | 36 | 47·4 | 81 | 25·75 |
| Skin .. .. | — | 7 | 11 | 10 | 8 | 6 | 1 | 43 | 50 | 75·5 | 26 |
| "Rodent ulcer" | 2 | 2 | 8 | 6 | 2 | 1 | — | 21 | 42·5 | 66 | 14 |

several years ago, I pointed out that this was a mistake; and that the sarcomata, like the epitheliomata, become progressively more frequent with advancing years.

I then expressed myself as follows:[1] "The sarcomata may arise at any period of life: a certain number of cases are congenital; more are met with in early infancy, especially during the first five years, than at any period prior to the twentieth year; after which sarcomata increase in frequency until middle life, becoming rarer again in old age." Thus, there is a certain general resemblance in the age incidence of the two types of malignant disease; whence also may be inferred a certain ætiological kinship, to which I specially directed attention, in these words:

[1] "Twentieth Century Practice of Medicine," 1898, vol. xvii., p. 487.

"It will be gathered from what has been stated, that there are close analogies between the two diseases—sarcoma and carcinoma—such differences as are noticeable being due to diversity of origin and its consequences, rather than to any essential difference in the nature of the morbid process."

Nearly all of the malignant tumours of early life are sarcomata; malignant epithelial tumours are, at this period, of exceedingly rare occurrence: thus, of 941 malignant tumours consecutively under my observation, 806 were of the epithelial type and 136 sarcomatous; in only 1 of the former did the disease originate under twenty years of age, whereas the latter furnished 24 cases. It is just at these early periods of life, that the age incidence of the two types of malignant disease is so different.

The following analysis of consecutive hospital cases tabulated by me, based on the age at the *onset* of the malady, makes this very clear :—

## TABLE VII.

SHOWING THE AGE INCIDENCE, AT ONSET, OF SARCOMA IN BOTH SEXES.

| | Under 5 Years. | 5- | 10- | 15- | 20- | 25- | 35- | 45- | 55- | 65- | 75 and upwards. | Total. | Aver. | Max. | Min. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Males .. | 2 | 2 | 6 | 6 | 7 | 22 | 10 | 20 | 16 | 8 | 1 | 100 | 40·4 | 79 | 2 |
| Females .. | 7 | 1 | 6 | 8 | 12 | 13 | 11 | 25 | 11 | 5 | 1 | 100 | 36·7 | 78·4 | 0·5 |

It is mainly owing to the comparative frequency of sarcomata during early life, that the average age of sarcoma patients, at the onset of the malady, is more than ten years earlier than the corresponding averages for those with malignant epithelial tumours; and, to the same cause, may be ascribed the greater precocity of the disease in female than in male sarcomatous patients, as displayed in the above table.

The national mortality returns for the year 1903, supply the following information on this subject, based on 1,789 cases.

## TABLE VIII.

SHOWING THE AGE DISTRIBUTION, AT DEATH, OF SARCOMA

| | Under 5 Years. | 5- | 10- | 15- | 20- | 25- | 35- | 45- | 55- | 65- | 75- | 85 and upwards. | Total. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Males .. | 58 | 33 | 21 | 38 | 42 | 93 | 138 | 169 | 183 | 107 | 44 | 3 | 929 |
| Females .. | 36 | 24 | 18 | 33 | 34 | 80 | 110 | 171 | 178 | 123 | 45 | 8 | 860 |

The differences between these mortality data, and those based on the age at onset of the malady, may be mainly attributed to the relatively long duration of life, in a large proportion of the sarcoma patients.

Here I take the opportunity of pointing out, that the age incidence of that interesting malady "chorio-epithelioma" *vel* "deciduoma malignum," the precise nosological status of which has yet to be determined, is far more akin to the connective-tissue type of malignant tumour than to the epithelial type; and, in a subsequent chapter [1] I shall show that the indications derived from study of its local, lymph-gland, and general dissemination are of similar import.

Considerations of this kind ought not to be neglected, in determining the nosological status of this somewhat anomalous and newly-described malignant growth: they are probably more reliable than the conclusions derived merely from histogenesis, which make this way and that way, according to the prepossession of the moment, this part of the subject still being involved in great obscurity, notwithstanding the dogmatic assertions of the predominant authorities, who appear to me to have based their present conception too exclusively on the histological appearances.

Teacher's analysis [2] of 170 cases shows that the average age of those affected with this malady was thirty-three years: the decennial incidence was as follows:—

| Age-Periods. | Cases. |
|---|---|
| 17 to 20 years .. .. .. .. | in 6 |
| 21 ,, 30 ,, .. .. .. .. | ,, 73 |
| 31 ,, 40 ,, .. .. .. .. | ,, 54 |
| 41 ,, 50 ,, .. .. .. .. | ,, 28 |
| 51 ,, 55 ,, .. .. .. .. | ,, 9 |

In twenty-two cases, the patients were over forty-five years old.

Since malignant epithelial tumours are hardly ever met with under the age of twenty, it may be concluded that nearly all the early-life malignant tumours, tabulated in the national mortality returns, belong to the sarcomata.

The following table, compiled from data supplied by the Registrar-General's Annual Reports, shows the age incidence of sarcoma in early life, for both sexes, during the latter half of the nineteenth century, and some other interesting particulars:

## TABLE IX.

SHOWING THE DEATH-RATES FROM MALIGNANT TUMOURS IN EARLY LIFE, PER MILLION PERSONS LIVING, FROM 1851-1860 TO 1891-1900.

| Age-Periods. | Under 5 Years. | 5- | 10- | 15- | 20- | All Ages. |
|---|---|---|---|---|---|---|
| **Males.** | | | | | | |
| 1851-1860 .. .. .. .. | 21 | 10 | 8 | 16 | 27 | 195 |
| 1861-1870 .. .. .. .. | 13 | 8 | 7 | 18 | 26 | 242 |
| 1871-1880 .. .. .. .. | 13 | 7 | 8 | 16 | 27 | 312 |
| 1881-1890 .. .. .. .. | 21 | 11 | 12 | 23 | 37 | 430 |
| 1891-1900 .. .. .. .. | 33 | 18 | 19 | 32 | 51 | 600 |
| **Females.** | | | | | | |
| 1851-1860 .. .. .. .. | 23 | 9 | 9 | 18 | 30 | 434 |
| 1861-1870 .. .. .. .. | 13 | 7 | 7 | 16 | 32 | 519 |
| 1871-1880 .. .. .. .. | 12 | 7 | 7 | 14 | 36 | 617 |
| 1881-1890 .. .. .. .. | 19 | 9 | 10 | 18 | 33 | 739 |
| 1891-1900 .. .. .. .. | 28 | 14 | 14 | 27 | 39 | 906 |

[1] Chapter XIX. [2] *British Journal of Obstetrics and Gynæcology*, 1900, vol. iv.

This table shows that there has been considerable increase in the mortality from malignant tumours, at these early periods, during the last two decennia of the nineteenth century; and, as at later periods, both sexes participated in this augmentation—which, however, affected males more than females.

### Congenital and Early-Life Tumours.

Less than half a century ago Virchow wrote:[1] "Hardly any cases of congenital sarcoma are known." Since then, vast additions have been made to our knowledge of the malignant tumours of early life; and hundreds of cases of congenital malignant disease have been reported. A large proportion of these early-occurring malignant tumours are undoubtedly congenital; that is to say, they originate during pre-natal life. Unfortunately, most of the records of these acquisitions are still buried in the archives of learned societies, where they are beyond the ken of practitioners; hence, even in treatises dealing specially with the diseases of children, little or nothing is to be found on this important subject. To remedy this deficiency, some years ago I unearthed and analysed a large number of these remarkable cases,[2] which have great significance for the correct appreciation of the ætiology of malignant disease in general, although the important indications thus furnished are still generally overlooked by pathologists.

In the course of this undertaking, I was specially impressed with the large proportion of these early-life malignant tumours, that obviously arise in connexion with pre-natal developmental irregularities; indeed, so many tumours of this kind are undoubtedly of congenital origin, that it seems not unreasonable to assume a pre-natal origin for the whole group. I thus became convinced, that tumour genesis is intimately connected with teratology—the stone which the builders of modern "tumour science" have so unwisely rejected.

As to the comparative frequency of the occurrence of pre-natal tumours, we have very little precise information; for, the bodies of infants have never been systematically submitted to post-mortem examination with this end in view, especially those of the prematurely born and the still-born.

Another noteworthy feature about the tumours of infancy and early life is, that the localities whence they are prone to originate, are very different from those whence malignant tumours commonly arise at later periods of life.

Thus, Duzan's[3] analysis of the records of 182 malignant tumours in early infancy, shows the following localization of the malady: eye in 70 cases, kidney 45, testis 11, prostate 8, bones 5, tongue 5, brain 5, abdomen 5, lung 4, dura mater 4, pancreas 3, liver 2, tonsil 2, rectum 2, the stomach in 1 case etc.

According to the larger analysis of Picot,[4] which embraces 424 cases,

[1] *Die krankhaften Geschwulste,* Bd. ii., S. 239. [2] *Lancet,* 1897, vol. i., p. 1194 *et seq.*
[3] "Du Cancer chez les Enfants," *Thèse de Paris,* 1876.
[4] "Les Tumeurs malignes des Enfants," *Rev. Méd. de la Suisse romande.* 1883.

the initial seats of the disease were as follows, in order of relative frequency :—eye and its annexes in 100 cases, kidney in 80, bones in 67, brain and its membranes in 31 (dura mater 6), abdomen and pelvis in 19, testis in 15, liver in 13, prostate in 8, skin in 8, intestine in 7, neck, tongue and ovary, each in 6 cases etc.

The relation of localization to age incidence in the malignant tumours of early life, is shown by the following analysis of 56 consecutive cases under my own observation : of these, 14 originated in the first quinquenniad viz., in the eye 7 cases, kidney 2, testis, inferior maxilla, base of skull, sacro-coccygeal region and tibia, each in one case ; in the second quinquenniad 6 cases originated viz., in the liver, parotid, kidney, tibia, cervical lymph-gland, and inferior turbinated bone, each in 1 case ; the third quinquenniad furnished 16 cases viz., in the inferior maxilla 4, femur 3, fibula 3, tibia, humerus, acromion process of scapula, parotid, thigh muscles, external ear, and retina, each 1 case ; in the fourth quinquenniad 20 cases arose viz., in the femur 4, superior maxilla 3, inferior maxilla 3, lymph-glands 2, testis, pharynx, kidney, parotid, base of skull, humerus, orbit and subcutaneous connective-tissue of the back, of each 1 case.

The great proclivity of infants to malignant disease of the kidney, stands in remarkable contrast with the extreme rarity of this kind of malady at later periods of life (only 32 cases in 8,378 primary malignant tumours).

Then, retinal gliomata are peculiar to early infancy, being rare after the fifth year, and after puberty they hardly ever arise ; and, of eight cases within my own experience, in four the disease was of congenital origin.

The scapula is remarkable among the skeletal bones, for the early age at which malignant tumours originate from it, and for their frequency ; thus, of 25 bone sarcomata in young infants, tabulated by Poinsot,[1] in 11 the scapula was the part affected, and congenital cases have been met with.

In contrast with this proclivity of the scapula to malignant tumours in early infancy, the long bones are rarely affected in this way, until the third quinquenniad, when a large number of cases arise : thus, of Gross'[2] 147 cases, only 3 arose during the first quinquenniad, and 3 during the second ; whereas 45 cases originated between the ages of ten and twenty years : similarly, of 119 cases tabulated by Butlin and Colby,[3] only 3 belong to the first quinquenniad and 3 to the second ; whereas, 35 originated between the ages of ten and twenty years.

These examples of extreme diversity in age incidence, according to localization, suffice to show the futility of attempts to illustrate the age incidence of sarcoma in general, by calculating the death-rates at different age-periods on the basis of certain selected sites, after the manner adopted by Bashford ;[4] for, supposing renal or retinal cases to predominate in such selections, the death-rate for the period of infancy would thus be inflated out of due proportion etc.

[1] *Rev. de Chir.*, 1885, t. v., p. 201.
[2] *American Journal of the Medical Sciences*, July, 1879, p. 24.
[3] Bartholomew's Hospital Reports, 1895, p. 31.
[4] Scientific Report of the Imperial Cancer Research Fund, 1905, part i., No. 2, p. 30

We are now in a position to discuss the interesting question, as to the earliest age at which malignant epithelial tumours may occur.

In this connexion, it must be remembered that the sharp distinction now made between epithelioma and sarcoma, is of comparatively recent origin. Many instances of congenital and early-life malignant tumours, containing epithelial elements, have been met with, especially in the renal, testicular, ovarian, gastric, hepatic and intestinal regions; and, such tumours have often been described as epitheliomata. With regard to such cases, it seems probable that the contained epithelial elements play but a secondary part; and that all tumours of this kind really are sarcomatous.

In other examples of alleged epithelioma in early life, the diagnosis has been based too exclusively on the microscopical appearances, the clinical features of malignancy being conspicuous by their absence. Instances of this kind have been published in connexion with the skin, lips, tongue, external genitalia etc.

In short, I conclude that pre-natal life, infancy and childhood, are completely exempt from malignant epithelial tumours.

The earliest age at which epithelioma has been satisfactorily demonstrated is eleven years, the patient being a girl with cylinder-celled cancer of the rectum; [1] and I have myself met with rodent ulcer in a young woman, in whom the disease began at the early age of fourteen years.[2]

In spite of a few exceptional cases of this kind, it may be safely asserted that, under the age of puberty, cancer is practically unknown.

In further illustration of these remarks, I propose briefly to discuss the available evidence, in relation to such representative localizations as the rectum, stomach, uterus and mamma.

The *rectum* is remarkable for the comparatively large number of malignant epithelial tumours, that arise from it during early life. Moreover, as previously mentioned, the earliest duly authenticated example of epithelioma hitherto recorded, has been met with in this situation. The number of cases of rectal epithelioma—in which the disease originated under twenty years of age—that might be cited, is considerable.

The following examples of which I have cognizance will suffice to illustrate this: two cases of columnar epithelioma in boys twelve years old, by Milne [3] (colloid) and Allingham; [4] at thirteen, by Czerny [5] (boy) and Michaux; [6] at fifteen, by Godin; [7] at sixteen, by Lazarus-Barlow; [8] at seventeen, cases by Schoening,[9] Cripps [10] and others. At later periods, under twenty, the recorded cases are so numerous as to render detailed references unnecessary.

In early life, malignant tumours of any part of the *gastro-intestinal tract* are of great rarity: thus, of 2,000 necropsies on children analysed by

[1] Stern, *Deutsche med. Woch.*, 1892, No. 22.
[2] *British Medical Journal*, 1890, vol. ii., p. 895. [3] *Ibid.*, 1905, vol. ii., p. 925.
[4] "Diseases of the Rectum," 4th edit., p. 270.
[5] *Münch. med. Woch.*, March 17, 1896, No. 11.
[6] Transactions of the Academy of Medicine of Richmond, Virginia, U.S., July 8, 1890. [7] Cited in Mollière's "Traité des Maladies du Rectum," etc.
[8] *Archives of Middlesex Hospital*, 1904, vol. ii.
[9] *Deutsche Zeits. f. Chir.*, 1885, Bd. xxii., Heft 1 and 2.
[10] *Lancet*, 1884, vol. ii., p. 67.

Steiner and Neureutter, not a single instance of malignant disease of the stomach was met with. Some idea of the extreme infrequency of gastric epithelioma at this period, may be gathered from the fact, that of 2,075 cases tabulated by Welch, only 2 originated under the age of twenty years.

However, several alleged examples of this kind have been reported in infancy; and 2 cases are said to have been congenital.

Congenital hypertrophy of the pylorus—not a very rare condition judging from the numerous cases lately recorded—has often been mistaken for infantile malignant disease, as in cases reported by Williamson [1] and others; and thus most of these anomalous tumours may be explained.

Congenital adenomata are occasionally found in the stomach, as in cases reported by Hueter, Schmorl and others. These growths are of innocent nature; but they occasionally originate sarcomatous disease. Kuhn [2] has described a case of this kind, in a female infant two years old, as "adenoid cylinder-celled cancer." A commoner occurrence is for inflamed tumours of this kind to be mistaken for malignant disease, as in Cullingworth's [3] case of so-called congenital epithelioma of the pylorus. Ashby and Wright's [4] case of "columnar epithelioma" of the pylorus etc., in a child eight years old, seems to me to belong to the same category.

The earliest duly authenticated example of a malignant epithelial tumour of the *stomach*, is N. Moore's case; [5] the patient being a girl thirteen years old, who died cachectic, with a large tumour projecting into the stomach, which grew from the gastric wall near the œsophageal orifice, and histologically proved to be "alveolar cancer."

Other instances of gastric epithelioma, in the second decade, have been reported by Scheffer [6] (pylorus) at fourteen, by Jackson [7] at fifteen, by Lidner and Kuttner [8] at sixteen, by Köster, [9] Landouzy, [10] Hirtz, [11] Boas [12] and others at seventeen, by Anning [13] at nineteen etc.

Under the age of twenty, malignant epithelial tumours of the *uterus* are hardly ever met with; and they are unknown prior to puberty.

Of 500 consecutive cases in my list, the earliest age at onset was twenty-two and a quarter years. By massing the statistics of several Continental and English authors, Gusserow obtained a total of 3,385 cases; and of this large number, only 2 originated under twenty.

The earliest age at which the outbreak of uterine epithelioma has been duly substantiated, is seventeen years; Schauta [14] and Glatter [15] have each recorded an instance of this kind—the cervix being the seat of the disease, which was glandular epithelioma.

[1] *London and Edinburgh Monthly Journal of the Medical Sciences*, 1841, vol. i., p. 23.
[2] *Berlin. klin. Woch.*, 1886, No. 27.
[3] *British Medical Journal*, 1877, vol. ii., p. 203.
[4] "Diseases of Children," 1905, 5th edit., p. 118.
[5] Transactions of the Pathological Society, London, 1885, vol. xxxvi., p. 195.
[6] *Jahrb. f. Kinderkeilkunde*, 1880, Bd. xv., S. 425.
[7] Cited by Osler, "Cancer of Stomach," 1900, p. 19.
[8] *Cent. f. d. Grenzgebiete d. Med. u. Chir.*, Bd. i., Nr. 12.
[9] *Cent. f. Chir.*, 1888, S. 372. [10] *Bull. de la Soc. Anat. de Paris*, 1872, p. 27.
[11] *La Méd. Moderne*, July 26, 1896.
[12] Cited by Osler, "Cancer of the Stomach," 1900, p. 19.
[13] *Lancet*, 1902, vol. ii., p. 1386. [14] *Wien. klin. Woch.*, 1880, Nos. 37 and 38.
[15] *Deutsche Vierteljahresschrift f. öff. Gesundheitspflege*, 1870, Bd. ii., S. 161.

Mundé [1] and Spinelli [2] have reported cases at eighteen; Beigel,[3] Eckhardt [4] and Tschop [5] have each met with the disease at nineteen, and Billroth [6] at twenty.

Several instances of so-called cancer of the uterus, at much earlier periods, have been recorded; but, in none of them has the cancerous nature of the affection, been satisfactorily established.

In Ganghofner's [7] case of so-called cancer of the portio, in a girl only nine years old, the eroded papillary outgrowth was more like a non-malignant "cauliflower excrescence"—of which several instances have been met with in infancy and childhood—than cancer. The clinical history accords with this; for, although the disease was of over two years' duration, it was localize . ; and there was complete absence of dissemination.

The instances of so-called cancer of the uterus by Heckford at nine months, by Rosenstein at two years, by Laidley at two and a half years, by Barnes at ten, by Simpson at twelve, and by Zweifel at thirteen years, were evidently sarcomatous.

The first four quinquennia of life are completely exempt from malignant epithelial tumours of the *mamma;* at least, I know of no well-authenticated case, that can be cited as having occurred within this period.

Of 500 consecutive cases under my own observation, the youngest was twenty-four years of age at the onset of the malady; and of 1,622 similar cases tabulated by Gross,[8] the earliest age was twenty-one years. The onset of mammary cancer before twenty-five is a great rarity. The earliest duly authenticated cases known to me, are Bryant's [9] at 20·5, and Henry's [10] at twenty-one years.

Alleged examples of malignant epithelial mammary tumours by Lyford at eight years, Carmichael at twelve, Cooper at thirteen, Howe at fifteen etc., were never histologically verified, so that we may safely assume that in these cases the disease was really sarcomatous, of which examples have been reported by Chambert at four months, by Vierregge in an infant, and by Gross at nine years.[11]

Turning now to the other extreme of life, I find that in advanced old age, malignant epithelial tumours seldom originate. The published cases of this kind are not very numerous.

The oldest patient known to me is the woman referred to by the Registrar-General, in his Report for 1883, who died, aged 106 years, with "cancer of the eye and wrist," as previously mentioned.

[1] Thomas' "Diseases of Women," 1891, p. 569.
[2] *Riv. clin. d. Univ. di Napoli,* 1890, xi., p. 75.
[3] Cited by Gusserow, *Die Neubildungen des Uterus,* 1885, S. 211.
[4] *Arch. f. Gyn.,* 1887, Bd. xxx., S. 471.
[5] *Gaz. hebd. Méd. de la Russie Méridionale,* 1896, No. 7.
[6] "Surgical Pathology," Hackley's translation, 1879, p. 694.
[7] *Zeits. f. Heilkunde,* 1888, Bd. ix., S. 337.
[8] *International Journal of the Medical Sciences,* March, 1888, p. 220.
[9] Guy's Hospital Reports, 1891, p. 337.
[10] *Statist. Mittheil. über den Brustkrebs* (I. D. Breslau, 1879).
[11] For references *vide* my book on "Diseases of the Breast."

A similar case is that of a lady, under the care of Coker,[1] who died aged 106, of epithelioma of the tongue.

Briggs[2] has met with epithelioma of the left cheek in a woman 103 years old; and Jalland,[3] the same disease of the lower lip, in a man 102 years old.

Bryant[4] has seen a malignant epithelial tumour of the female breast, which was first noticed at the phenomenal age of ninety-six; Lunn[5] has described a similar tumour of the mamma, in a man aged ninety-one; and Gurlt[6] cancer of the stomach, in a man aged ninety-two.

An instance of epithelioma of the cervix uteri, in a woman aged ninety-three years, has been reported by Findley;[7] and several cases of this form of malignant uterine disease, at ninety years and upwards, have also been recorded.

With regard to malignant epithelial tumours in general, it may be stated that under the age of puberty, they are practically unknown: during the fourth quinquenniad a few cases may exceptionally be met with, but its occurrence before twenty-five is a great rarity. In the third decennium more cases occur, but their number is still small. Subsequently the numbers rise with increasing frequency up to sixty-five, when they attain their maximum. After seventy-five the disease is much rarer; and, at more advanced ages, the falling-off is still more marked.

To sum up: we learn from the foregoing facts, that while the forces of growth, development and reproduction are in greatest activity—during the periods of pre-natal life, infancy, childhood, adolescence, and adult age—the tendency to malignant tumours of any kind is exceedingly small. In both sexes, the disease begins to be frequent, as soon as the period of perfection has been attained, *i.e.*, after the thirty-fifth year; during middle age and the decline of life the proclivity to it increases, until about the sixty-fifth year; after which it becomes relatively less frequent, and increasingly so as age advances.

The principles that govern the age incidence of malignant disease in general, apply also to its various local manifestations in both sexes. That some parts of the body—such as the uterus, ovary and mamma—are attacked earlier than others, may be ascribed to the fact that the former attain maturity earlier than the latter.

The general rule for the uterus, ovary, breast and all organs is, that their liability to malignant disease begins with the decline of their functional activity, and increases while this is progressing.

Thus the liability to malignant disease waxes, as the developmental and reproductive activities wane. The antagonism between the forces of growth, development and expenditure is the same in pathology, as in physiology. It is owing to the varied interactions of forces thus called into existence, that the constitution is so different at different periods of life; and that each period has its special morbid proclivities.

[1] *British Medical Journal*, March 5, 1887: "Additional Report on Centenarians."
[2] *St. Louis Medical and Surgical Journal*, U.S., 1887, vol. liii., p. 150.
[3] *British Medical Journal*, May 9, 1891. [4] "Diseases of the Breast," 1887, p. 149.
[5] Transactions of the Pathological Society, London, 1897, vol. xlviii., p. 247.
[6] *Arch. f. klin. Chir.*, 1880, Bd. xxv., S. 420.
[7] *American Journal of Obstetrics*, etc., February, 1902, p. 524.

Type, variation and correlation, all change with the age of the individual. At present we know hardly anything, as to the nature of the metabolic reactions underlying these changes; but it is to the physiological chemist that we must look, for clearing up this difficult problem.

In a general way, it may be said that integrative changes predominate during the earlier part of the developmental cycle, when growth is most active; alternate excesses of integrative and disintegrative activities, characterize its middle part; and, as the cycle nears its terminus, the latter manifestations tend to predominate. It is as the outcome of disturbances in the rhythm of growth, during these post-meridian stages, that malignant and other tumours are most prone to arise. Thus these belong to the disintegrative order of activities.

In this we have an illustration of the universal biological law, that growth varies according to the surplus of nutrition over expenditure. So long as the surplus exists—that is to say, while nutrition is relatively high—simple continuous growth is maintained; but, when nutrition is relatively low—that is to say, when it is nearly equalled by expenditure—new centres of development are apt to arise, and growth tends to become *discontinuous*.

Changes of nutrition determine the transition from the one to the other mode of growth. To the operation of such causes, as I have elsewhere maintained,[1] the origin of malignant and other neoplasms must ultimately be ascribed.

[1] "The Principles of Cancer and Tumour Formation," 1888; also Chapters VII. and IX. of the present work.

3 20/pm

## CHAPTER XVI

# ÆTIOLOGICAL INDICATIONS DERIVED FROM THE STUDY OF THE LIFE-HISTORY OF CANCER PATIENTS

### Nutrition and Cancer.

In preceding chapters[1] I have instanced many facts, which indicate that the causation of cancer is intimately connected with nutrition and the conditions of existence; and it is especially such influences as are comprised under the terms alimentation and domestication, that seem to me to be of paramount importance.

I have now to refer to some other items of information, bearing on this subject.

Long-continued observation of cancer patients, in the early stage of the disease, has convinced me, that most of those affected are large, robust, well-nourished, florid persons, who appear to be overflowing with health and vitality. Such persons have large appetites, good digestions, and exceptionally large assimilative power; hence they often present a considerable amount of *embonpoint*. Mr. and Mrs. John Bull, as so frequently depicted in the pages of *Punch*, are the physical types of the majority of cancer patients. Such types are indicative of general hyper-nutrition.

Careful study of the life-history of centenarians and of persons of advanced age—who, as we have seen,[2] are very rarely the victims of cancer—shows that they are generally of spare figure, medium height, and that they eat frugally, taking but little meat and alcohol. The bulky, overfed type of being, seldom attains to great age. This is probably the explanation of the rarity of cancer in the aged, to which I have previously referred; and in like manner it is alleged that the monks and nuns, who lead abstemious lives and eat little or no flesh food, rarely succumb to this disease.

### The Cancer Type.

Beneke[3] has described those predisposed to cancer as having large hearts and wide arteries, with small lungs and pulmonary artery;[4] long, large and capacious intestines, with well-developed osseous and muscular systems, and abundant adipose tissue. This quite accords with what I

[1] Chapters II., III., IX., and XV. [2] Chapter XV.
[3] "Constitution und constitutionelles Kranksein des Menschen," Marburg, 1887.
[4] Here it may be mentioned that in the tuberculous—as indicated by Fothergill and others—just the converse obtains—viz., small heart and large lungs—thus adding one more to the list of contrasts furnished by the subjects of these two maladies.

have myself observed, that cancer patients usually are of a coarse physical type. Those recently attacked never present a cachectic appearance. The small, pale, ill-nourished women, of the type so familiar in Lancashire and other large industrial centres, where women-workers abound, are seldom the victims of this disease.

It has lately been argued by Cattin,[1] that there is some connexion between hypoplasia and cancer ; but, with the exception of the smallness of the lungs and pulmonary artery, to which I have just referred, I have never met with anything that could be adduced in favour of such a suggestion. No doubt persons with imperfectly developed and prematurely exhausted sexual organs are unduly prone to cancer, as I have had occasion to indicate in a previous chapter,[2] and it is in this category that most of the cases cited by Cattin should be included ; but, these cases form a special group, and it is unquestionably true that the majority of cancer patients have a well-developed sexual system, as is proved by the large proportion of them who marry and are prolific.

## Obesity.

It was a prevalent belief in former times, that the obese were unduly prone to cancer, and it ought not to be difficult for those who have opportunities of studying the life-history of the obese, to thoroughly test this matter ; but I am not at present aware of any satisfactory data bearing on the subject.

The connexity between obesity and cancer, was long ago remarked on by J. H. Bennet,[3] who says : " If a tendency to fat be an antidote to tubercle, as I believe it is, spareness may possibly be considered opposed to cancer. In the one case, we should do all we can to bring the nutrition up to and above the average : in the other, down to or below it." Elsewhere he adds : " The circumstances which diminish obesity and the tendency to the formation of fat, seem to be opposed to the cancerous tendency." I believe there is a sufficient amount of truth in these suggestions, to justify me in reproducing them here ; at any rate, the obese are high feeders and great meat-eaters, and they are seldom the victims of tubercle.

I have seen a statement by R. Bell,[4] to the effect that the thyroid is invariably more or less atrophied in cancer patients ; but what validity attaches to it, I am unable to say. The suggestion should, however, receive the attention of pathologists, with the view of confirming or confuting it, especially as some obesity is often a characteristic of the cancerous.

## Blood-Pressure.

Lately considerable attention has been given to the rise of the blood-pressure in later life—which is generally associated with, and perhaps caused by, sedentary habits, excess of food, and perverted metabolism—

[1] *Jowin. de Méd. et de Chir. pratiques*, April 10, 1905. [2] Chapter IX.
[3] " Cancerous and Cancroid Growths," Edinburgh, 1849, p. 251.
[4] *New York Medical Record*, February 16, 1907, p. 260.

and some authors have maintained that conditions of this kind give proclivity to cancer. There has certainly been great increase in the mortality from diseases of the circulatory system, during the last half-century, especially at age-periods above the thirty-fifth year, and it is probable that the conditions responsible for this increase, are similar to those which predispose to cancer; but, it has not yet been proved, that the cancerous are more prone to increased blood-pressure than the non-cancerous.

According to my investigations, however, cancer patients are unduly prone to heart disease; and I have also found that the relatives of cancer patients have special proclivity to apoplexy, heart disease, rheumatic fever and other arthritic manifestations.

It has been suggested, that the abandonment of venæsection has played a part in the increase of this type of disease and of cancer, and it well may be so; but nothing of the nature of proof has been adduced in this connexion.

### Diabetes.

It is well known that malignant tumours are rich in glycogen; and that the blood of those who bear these tumours, contains an excess of sugar-forming substances.[1] Of late, many instances have been reported of the concurrence of malignant tumours and diabetes (Boas, Kappeler, Kreutzmann, Tuffier etc.); and, it has been suggested, that the diabetic state favours their development. On the other hand, the diabetic state was very seldom noticed in the numerous cancer patients under my own observation; and other pathologists have also remarked on the rarity of this conjunction. Even when the pancreas is the seat of malignant disease, diabetes is far from common.

Boas,[2] however, reports that of 366 patients with intestinal cancer tabulated by him, 12 were also affected with diabetes.

Of 62 examples of this concurrence, collected by Kappeler,[3] the seats of the cancerous disease were as follows:—breast in 18, mouth 12, stomach or liver 12, uterus 3, rectum 2, colon and ovary each in 1 case etc.

Frerichs, having noted the cause of death of 200 diabetic patients, found that 6 had died cancerous, which is a very small proportion.

During the last half-century, the mortality from diabetes has greatly increased in our country, and so also has the amount of sugar consumed as food.

Finally, it may be mentioned that diabetes is a disease to which the Jewish race is specially prone; but, as we have already seen, their proclivity to cancer is rather less than that of non-Jews.[4]

Thus, there is lack of conclusive evidence as to any definite ætiological relationship between the diabetic state and cancer; but, diabetics are known to be unduly prone to tubercle.

[1] According to Gulland, the blood of cancer patients, in the early stage of the disease, is free from glycogen; although, when the malady is advanced, this substance abounds in it (*British Medical Journal*, 1904, vol. i., p. 880).

[2] *Berlin. klin. Woch.*, March 16, 1903.

[3] *Thèse de Paris*, 1898.

[4] Chapter II.

## Arthritism.

I believe it is owing to the researches of Verneuil, Isch-Wall and others of this school, during the latter part of the nineteenth century, that some connexion was first shown to exist between arthritism and cancer. My researches certainly show, that the members of cancer families are unduly prone to arthritic manifestations — especially to rheumatic fever and heart disease; thus, of 267 female cancer patients under my observation, 24 had previously suffered from rheumatic fever, and nearly as many from other rheumatic affections: and of 160 similar cases analysed by Nunn, arthritic affections were traced in 15. There is also evidence of a considerable amount of rheumatic fever and heart disease, among the brothers and sisters of the cancer patients in my list; moreover, of 154 parents of these patients, 12 had died of heart disease, or 1 in 12·8, whereas in the general community, at that time, the corresponding ratio was 1 in 79; from rheumatic fever my analysis shows 1 death in 154 parents, the corresponding ratio for the community at large being 1 in 195.

Here it may be mentioned, as I shall subsequently have occasion to prove, that gall-stones are of more frequent occurrence in the cancerous than in the non-cancerous.

The Bonaparte family furnishes a concrete example of the connexity of these morbid conditions, Pierre having died from heart disease consequent on rheumatic fever, and Napoleon III. from stone in the bladder: two other members of the family, Jerôme and his son Napoleon, suffered from diabetes; while Napoleon I., his father, his brother Lucien, and his sisters Caroline and Pauline, all died from cancer of the stomach.

According to Charcot, "Heberden's nodes"—which he regards as pathognomonic of the rheumatic diathesis—are not uncommonly met with in the subjects of mammary, uterine and some other local forms of cancer; and we know that severe forms of heart disease are comparatively frequent, in those who bear these stigmata.

It has been suggested by Haig, that the special factor in arthritism which gives proclivity to cancer, is an excess of uric acid in the tissues; but not the slightest evidence has been adduced in support of this contention.

Finally, there are good reasons for believing the arthritic predisposition to be in some way antagonistic to tubercle, as is specially obvious in the case of the gouty.

## Osteitis Deformans.

Some years ago, Paget[1] published an account of: "A form of chronic inflammation of bones (*osteitis deformans*)," which was often complicated by malignant tumour; this was the condition in three of his five cases. Other examples of this concomitancy were subsequently reported by Cayley, Goodhart, Howse, Lunn etc., so that the impression arose that this form of bone disease was often complicated by cancer.

[1] Transactions of the Medico-Chirurgical Society, London, 1877, vol. lx., p. 37.

With regard to this, I have to point out that of over 1,000 cases of malignant disease investigated by me, and of which I now have the records, not a single one was complicated by osteitis deformans: in this list 170 cases of breast cancer in women, and 160 cases of uterine cancer are comprised.

In most of Paget's cases, as well as in those subsequently reported, the malignant tumours affected the skeletal bones; and, it seems probable, that this malady should be classed with the recently discriminated "multiple myeloma," whether associated with albumosuria or not.

## Gall-Stones.

In this place reference must also be made to the incidence of gall-stones, which certainly are of more frequent occurrence in the cancerous than in the non-cancerous.

According to Brockbank, in England, gall-stones are met with in 4·4 per cent. of the hospital inmates—males 2·9 and females 7·9 per cent. Among the whites of the United States, Mosher found that the records of 1,037 necropsies yielded 7·85 per cent. of gall-stones—males 5·49 and females 9·37 per cent. In this country, according to Rolleston, gall-stones are present in 8·5 per cent. of all necropsies on adults; and, according to Kehr, in 10 per cent.[1]

On the other hand, in the cancerous, Muir found gall-stones in 13 out of 103 necropsies, or in 12·6 per cent.; of 67 men in 7·9 per cent., and of 40 women in 20 per cent.

Of 281 cancer necropsies analysed by me (in which no hepatic or gastric cancers are included), gall-stones were noted in 18, or in 6·4 per cent.: 100 were men, with gall-stones in 4 cases; and 181 women, with gall-stones in 14, or 7·7 per cent.

It is generally believed that gall-stones are more frequently found in association with cancer of the stomach and liver, than with any other of the local manifestations of the disease; and, it accords with this, that in a series of cancer necropsies comprising a due proportion of these localizations, Colwell found gall-stones two and a half times as frequent in the cancerous as in the non-cancerous.

Thus the cancerous, like the tuberculous and the insane, are more prone to gall-stones than the generality of the population of corresponding age and sex.

As further evidence of the perverted metabolism commonly associated with the predisposition to gall-stones, it may be mentioned that of 115 necropsies on the bodies of persons thus affected, Mosher found marked arterio-sclerosis in 50.

According to Murchison, the tendency to gall-stones is fairly often associated with proclivity to urinary gravel.

Gall-stones are believed to be of more frequent occurrence among the rich, than the poor; while the obese and those of sedentary habits, are said to be specially liable.

[1] *Vide* also Chapter XI.

### Tubercle and Cancer.

In some of the earlier chapters of this work,[1] I adduced a mass of detailed information, as evidence of the fact that, in temperate climates, the incidence of tubercle and cancer is determined by the local conditions of existence, in such wise that tuberculous diseases are rarest where cancer is most prevalent and *vice versâ*. In tropical countries malaria may be regarded as taking the place of tubercle.

Another fact elicited was, that the great increase of cancer during the last half-century, has coincided with remarkable decline in the mortality from tuberculous diseases—especially phthisis; and it was shown that this connexity also was due to variation in the local conditions of existence, with respect to which these two maladies are inversely related.

When treating of the family history of cancer patients in a subsequent chapter, I shall adduce evidence to show that a large proportion of cancerous persons are the surviving members of tuberculous families; and, it is this heritable condition, that gives such persons their special proclivity to malignant disease, when exposed to certain conditions of existence. In short, I think there can be no doubt, that those who survive the peculiar kind of degeneracy associated with the tuberculous predisposition, are at a later period of life specially prone to cancer.

At first sight, there may seem to be some difficulty in reconciling this conclusion, with the appearance of rude health which, as I have shown, characterizes most of those predisposed to cancer; but in reality there is here no contradiction, for it commonly happens that the surviving members of tuberculous families, although they never develop cancer, are remarkable for their robust appearance and longevity. The famous Astley Cooper was a striking example of this, yet he was of a very tuberculous family, having lost five near relatives from this disease; moreover, in his youth, he had hæmoptysis, which was rightly supposed to be due to pulmonary tubercle, for when—in accordance with his last instructions—his body was submitted to post-mortem examination, a healed tuberculous lesion was found at the apex of his lung.

The much greater frequency with which obsolescent tuberculous lesions are found in association with cancer, than with most other diseases, also tells in favour of this view.

Thus, of 136 consecutive necropsies on women under my observation who died of cancer (uterus 79, breast 44, rectum 13), obsolete pulmonary tubercle was found in 17, or in 12·5 per cent.; whereas, of 16,562 consecutive necropsies tabulated by Heitler,[2] on the bodies of those who had died in the Vienna Pathological Institute of various causes, which included but 110 cases of cancer, obsolete tubercle was met with only in 789 cases, or in 4·7 per cent.

In collecting these data, it is important to note that only well-marked, macroscopical, gross lesions, were taken into account; for, when modern microscopical methods of research are fully utilized, tuberculous lesions

[1] Chapters II., III., IV., and IX.

[2] *Wiener Klinik.*, 1879, S. 269.

can be demonstrated in almost every corpse, as the researches of Naegeli,[1] Brouardel and others have proved.

The outbreak of cancer often follows, or coincides with, the healing of tubercle.

Although these two diseases are thus shown to be intimately correlated, it is nevertheless very rare—considering the great frequency of both—to find cancer and tubercle in active progress in the same individual. I have met with this conjunction only twice in 136 cancer necropsies; and Kelynack,[2] at the Manchester Infirmary, found it only twice in 145 similar necropsies. Other analyses of this kind by various authors (Zahn, Moak, MacCasky, Boas etc.) give similar results. Hence, there is obviously decided antagonism, between active tuberculous and cancerous manifestations.

I am inclined to believe, as F. P. Weber has suggested, that in most cases of this concomitancy, the active tuberculous disease is due to the rekindling of old quiescent foci, by the lowering of the patient's general vitality, consequent on the progress of the cancerous disease.

It is evident from the foregoing indications, that active tuberculous disease is of very much less frequent occurrence in the cancerous, than in the non-cancerous.

With regard to tubercle in general—active as well as obsolete—there can be no doubt that the cancerous are less prone to it than the non-cancerous: thus, of 569 cancerous persons, Lubarsch [3] found that 20·6 per cent.[4] presented tuberculous lesions; whereas, of 5,967 non-cancerous persons, 42·7 per cent. were tuberculous; similarly of 65 cancerous persons, forty years old and upwards, Nicholls [5] found that 9 per cent. were tuberculous; whereas, of 279 non-cancerous persons of similar ages, 19 per cent. were tuberculous.

The available statistical data also indicate, that cancer is of much less frequent occurrence in the tuberculous, than in the non-tuberculous: thus of Lubarsch's 2,668 tuberculous cases, 4·4 per cent. were cancerous; whereas, of his 3,868 non-tuberculous cases, 11·7 per cent. were cancerous: similarly of Nicholls's 60 tuberculous persons, forty years old and upwards, 10 per cent. were cancerous; whereas, of his 243 non-tuberculous persons having the same age distribution, 22·2 per cent. were cancerous.

Considering the great frequency of both maladies, the comparative rarity of their coexistence is remarkable; and a certain antagonism is thus indicated, which, however, falls far short of absolute incompatibility.

A somewhat similar inverse relationship of tubercle and cancer is also noticeable in respect to site incidence; for tubercle very rarely originates in the localities where cancer commonly arises, and *vice versâ*. Thus the stomach, liver, uterus and mamma, the commonest seats of origin of cancer, are comparatively seldom the seats of primary

[1] *Arch. f. path. Anat.*, 1900, Bd. clx., S. 426. [2] *Medical Chronicle*, June, 1897.
[3] *Arch. f. path. Anat.*, 1888, Bd. cxi., S. 305.
[4] This is a higher percentage than most pathologists have found, *e.g.*, Kelynack 14·4, myself 14, G. Forbes 12·5, Le Goupils 8·3, Cohen 5, etc.
[5] *Montreal Medical Journal*, 1903, vol. xxxii., p. 333.

tuberculous disease ; and even secondary tuberculous manifestations, are uncommon in these localities : in short, over 80 per cent. of all malignant tumours, arise in localities where tubercle is seldom met with.

On the other hand, the lung—whence such an immense number of cases of primary tubercle arise—very seldom originates any form of malignant disease ; thus, only 17 cases of this kind are included in the 13,824 primary malignant tumours of my list. This consideration alone, suffices to negative K. Wolf's contention, that local tuberculous lesions of the lungs etc. create a predisposing cause to cancer.

Moak [1] has attempted to account for this antithesis, by calling attention to the different age incidence of the two maladies, maintaining that most cases of pulmonary tubercle are fatal before fifty ; and most cases of cancer after. To such a statement as this it may be objected—even if the facts were correct—that it would, nevertheless, not explain the antithesis. In so far, however, as the particular local forms of cancer above referred to are concerned, the correctness of the statement is certainly inadmissible ; for, the average age at death of cancer of the uterus, is forty-four years, of the mamma forty-eight, and of the stomach 47·4 for females, and fifty-one for males ; while, as to the mortality from tubercle of the lung, the national statistics show that this attains its maximum in the decennium thirty-five to forty-five.[2]

In this form of antithesis, as in the others I have had occasion to mention, the mutual antagonism falls far short of absolute incompatibility. Thus, instances of the coexistence of tubercle and cancer of the same locality etc., have been reported, *e.g.*, in the stomach (Claude) ; in the uterus (Wallert and Franqué) ; in the mamma (Moak, Kallenberger, Crawford and Warthin) ; in the liver (Frerichs) ; in the large intestine (Dalton, Zenker, Naegeli, and Moak) ; in the rectum (Naegeli and Baumgarten) ; in the small intestine (Lubarsch and Naegeli) ; in the larynx (Baumgarten, Zenker and Crone) ; in the lung (Batty Shaw, Schwalbe, Wolf, Wilson Fox and Friedländer) ; in the œsophagus (Cordua) ; in the eye-sarcoma (Silex) etc. Moreover, many instances of "lupous cancer" have also been described.

It will be gathered from the foregoing, that while the outbreak of cancer not unfrequently follows or coincides with the healing of tubercle, active tuberculous disease is very rare in the cancerous. Thus, while the *predisposition* to tubercle gives proclivity to cancer, there is, nevertheless, a certain antagonism between active tuberculous and cancerous manifestations, the special causative factors which favour the one being inimical to the other, and *vice versâ*.

I have dwelt at some length on the inter-relations of these maladies, because they appear to me to have an important bearing on the ætiology and prophylaxis of cancer ; and, so far as I know, the matter has never before been set forth in its true light.

[1] *Journal of Medical Research*, 1902, vol. viii., p. 128.

[2] An analysis of 161,920 cancer deaths, by Dr. J. F. Payne, shows that 83 per cent. of them took place before the age of forty-five ; while, of 361,000 phthisis deaths, only 24 per cent. took place after forty-five ("Cancer in Relation to Life Assurance," 1898).

## Pleural Adhesions, Emphysema, Cardiac Changes etc.

Post-mortem records show the great frequency of old adhesions of the pleuræ in the cancerous : thus, of my 79 necropsies for uterine cancer, old pleural adhesions were present in no less than 41 cases (general, 22—of which 20 were bilateral ; and, in 16 cases, these adhesions were confined to the region of the apex—both in 10, left 4, right 2) ; similarly, of 44 necropsies for mammary cancer in women, old pleural adhesions were noted in 24 cases (general in 16—of which 13 were bilateral ; and, in 8 cases, these adhesions were in the region of the apex).

Thus, of these 123 necropsies, old pleural adhesions were noted in 65, or in more than half of all the cases. Probably most of these pleural lesions were tuberculous in origin.

With regard to emphysema, of the 79 uterine cancer necropsies, this condition was noted in 23 : and of the 44 mammary cancer post-mortems in 12 ; thus, of these 123 necropsies, emphysema was present in 35, or 1 in every $3\frac{1}{2}$.

As previously mentioned, in the earliest stage of the disease, cancer patients have large hearts and wide arteries, with small lungs. The natural tendency is for the heart and arteries to increase in size from childhood to old age, as was long ago shown by Bigot and Clendenning ;[1] but, in those who have died from cancer, the heart is generally small and undersized, with corresponding diminution of the aorta and of the chief arterial trunks. These changes seem to be secondary to alterations in the blood, which take place during the course of the disease ; for, not only are its morphological, chemical and physical properties changed, but, as the experiments of Louis show, its total quantity is notably diminished.

To the combined operation of these factors, the diminished cardiac dulness so often noticeable in cancerous patients, to which Gordon[2] has lately called attention, may no doubt be ascribed.

## Malaria.

A few years ago Löffler,[3] reviving an ancient and wellnigh forgotten belief, suggested that there is an antagonism between malaria and cancer ; and proposed to treat the cancerous with injections of malarial blood.

The main support for this conception is derived from the fact, that malaria attains its maximum in the tropics, where cancer is rare ; moreover, proceeding from the equator towards the poles, as malaria diminishes, cancer becomes commoner.

As I have already intimated, this correlated variability is probably the outcome of changed conditions of existence, rather than of any specific antagonism between the two maladies ; and thus also may be explained the comparative rarity of tubercle in tropical countries.

In our own country, cancer is common enough among the inhabitants

[1] *Medical Gazette*, vol. xxii., p. 450.
[2] Transactions of the Medico-Chirurgical Society, 1904, vol. lxxxviii., p. 327.
[3] *Deutsche med. Woch.*, October 17, 1901.

of the malarious, marshy flats of the Essex coast and its vicintiy ; and, in malarious parts of Europe, similar conditions have been noticed. Moreover, cancer is of as frequent occurrence in malarious Italy, as in Ireland and Prussia, where malaria is almost unknown ; while in Holland, malaria and cancer are both common.

The occurrence of cancer has often been noted in malarious subjects. Thus, there can be no question of any marked incompatibility between the two diseases ; although it is not improbable that the impaired nutrition determined by chronic malaria, may be a condition unfavourable to the onset of cancer, but of this convincing evidence is lacking.

### Syphilis and Cancer.

In most modern communities syphilis is a common disease, at least as common as, or even commoner than, tubercle. Syphilis also has this peculiarity, that it generally stamps its victims with what Ricord has so well designated as "the signature of syphilis"—marks by which the expert can recognize its trail.

Well, I have looked for these marks, very carefully, in a large number of female cancer patients ; and I have very seldom been able to find any trace of them—signs of congenital syphilis being entirely absent.

Thus, of 165 consecutive female breast-cancer patients, not a single one presented undoubted signs of having had syphilis ; and, of 160 uterine-cancer patients, only one presented signs of having had syphilis.

Other indications furnished by careful study of the life-history of these patients clearly show, that they are seldom the victims of syphilis : thus, they marry earlier, have more children, and fewer miscarriages, than the majority of women of the same rank in life. The ensemble of the life-history of these cancer patients shows that they had almost invariably led regular, sober, industrious and healthy lives ; and not a single one of them had ever been addicted to prostitution, so far as I could ascertain.

I have never seen the slightest indication that would support Esmarch's contention,[1] as to sarcoma being a late manifestation of syphilis in the second or third generation ; and I believe it has no foundation in fact.

There can be no doubt that prostitutes, drunken and dissolute persons, notwithstanding their great proclivity to venereal and syphilitic affections, are less subject to cancer than the majority of women of their own rank of life.

Of like import is the fact that cancer is rarest in the slums of our large towns, where syphilis is commonest.

From the foregoing and from other indications of this kind, it may be inferred that the victims of constitutional syphilis, are much less prone to cancer than the non-syphilitic.

This comparative immunity of the syphilitic, is probably due to the depraved nutrition and lowered vitality, caused by contamination of the

[1] *Arch. f. klin. Chir.*, Bd. xxxix., Heft 1.

system with the syphilitic virus. Turenne was probably aware of this, when he syphilized his recently operated cancer patients, with the object of preventing recurrence.

Here it may be mentioned that cancerous diseases are met with in the animal world, where syphilis is unknown; so that syphilis cannot be regarded as the cause of cancer, as some have alleged.

In connexion with this subject, reference may be made to the immunity of these female cancer patients from *chronic ulcer of the leg*, of which there was not a single example among these 325 women. Considering the commonness of the latter affection in women over middle age, this immunity of these cancer patients is certainly highly remarkable.

In the eighteenth century, it was customary to establish "issues" on each of the four limbs, after operations for the removal of cancer, with the object of preventing recurrence "by opening a passage for the cancerous virus"; and, under the influence of similar ideas, the operation wounds were prevented from closing by first intention. It is probable that such methods do exert some deterrent influence on the disease, acting like the syphilitic virus—but less powerfully—by lowering the general vitality.

I have seen it stated that in Eastern Asia, syphilis and leprosy are generally regarded as antagonistic maladies; and, in Europe, the decline of leprosy has been concomitant with the rise of syphilis.

Before quitting this subject, it must be mentioned that a few very exceptional instances have been recorded, of cancerous disease arising from these chronic ulcers; and from various syphilitic and other lesions.

### Erysipelatous and Suppurative Affections.

It has been urged by Lambotte [1] and others, that erysipelatous and suppurative affections are of comparatively rare occurrence in the cancerous; and the inference has been drawn, that these maladies—by vaccinal action—protect from cancer.

In order to test the value of the alleged rarity of erysipelas in the cancerous—which is at variance with the impression I had formed after an extensive experience of cancer—I have examined the statistical data of some of the large London hospitals, with the following results.

Of 395 extirpations of the breast for cancer, 40 were subsequently attacked by erysipelas, or 10 per cent.; whereas, of 173 recent scalp wounds, under treatment at one of these hospitals during the same period, only 8 were attacked by erysipelas, or 4·6 per cent.

It would thus appear—as my own experience suggested—that instead of being immune from erysipelas, the cancerous are more than twice as prone to it as the non-cancerous.

Lambotte also states that there is seldom any evidence of suppurative affections, in the pathological antecedents of the cancerous.

As I was at some pains, several years ago, to determine the maladies to which the cancerous are prone, I find that I have at hand the requisite data for testing the validity of this statement.

[1] *La Presse Méd. Belge*, 1896, No. 21, p. 161; and No. 35, p. 274.

Thus, of 130 uterine-cancer patients under my observation, 9 had previously suffered from small-pox, 5 from phthisis, 2 from erysipelas, 2 from abscess, 2 from fistula-in-ano, and 1 each from necrosis, lupus and furunculosis.

Of 130 breast-cancer patients, 5 had previously suffered from phthisis, 4 from small-pox, 4 from ulceration of the uterus, 3 from erysipelas, 3 from old abscesses of the neck, and 1 each from fistula-in-ano, suppurative tuberculous disease of the knee-joint, otorrhœa and whitlow.

Thus, of these 260 female cancer patients, 46, or 18 per cent., had previously suffered from some form of suppurative disease.

To compare with the foregoing, I have found that of 75 women with non-cancerous tumours, 12 had suffered from previous suppurative diseases, or 16 per cent., as follows: phthisis 3, abscess 4, erysipelas 2, and 1 each from small-pox, ulceration of uterus and hip-joint disease.

From this it appears that Lambotte's second proposition is as unreliable as his first; for, as these data show, the cancerous are just as prone to suppurative diseases as the non-cancerous.

I have seen a great many cancer patients attacked by erysipelatous and suppurative affections; but I have never noticed consequent marked amelioration of the disease, much less anything approaching a cure. In many such cases, these superinduced affections led to a rapidly fatal issue.

I believe that most of the alleged cures of malignant disease by erysipelas inoculations etc. are attributable to diagnostic errors; at any rate, I am convinced, that tuberculous, syphilitic, and various other chronic inflammatory pseudo-plasms are often mistaken for malignant disease by experienced surgeons, especially in the uterus and breast; and, I suspect that cases of actinomycosis and other parasitic infections, are more frequently mistaken for malignant disease than is generally believed. Consequently, every new specific for cancer has no difficulty in producing a crop of "cures" to justify itself; although I am convinced that cancer has never really been cured, by any external application or internal medicament whatever.

As for those exceptional cases of malignant disease, in which—after an attack of erysipelas or after inoculation with its toxins etc.—arrest or diminution has been observed, evidently such conditions are not due to any specific or vaccinal action of the remedy, for similar effects have been produced by many widely different conditions.

For instance, many examples of the regression of mammary cancer, in connexion with acute outbreaks of pulmonary tubercle have been reported. Perrion has seen the same disease subside, after an operation for goitre, followed by much suppuration. Tealliér has noticed retardation in the progress of uterine cancer during lactation. An instance of the regression of mammary sarcoma, after artificially induced delivery, has been reported by Jahr. In cases of intra-abdominal malignant disease, Bidwell and others have seen marked amelioration ensue, after simple exploratory laparotomy. Beatson's cases of regression of mammary cancer after oöphorectomy evidently belong to this category. Similar results have ensued after injections of tuberculin, the toxins of erysipelas etc. Many other such instances might be cited. In the penultimate stages of the cancerous cachexia and most exhaustive illnesses, malignant growths often become stationary ; and even appear to wither and dry up, shortly before death. Blanchard and Fleury have reported instances of this kind, in connexion with uterine cancer etc.

The only feature common to all such cases is, the extremely debilitated condition to which the patients are reduced ; and I think there can be no doubt, that enfeebled vitality is the cause of such improvement as is noticeable. The condition of the patient is, in fact, similar to that brought about by the starvation treatment of cancer, as formerly practised with some success by Hufeland and others.

### Infectious Diseases.

By careful study of the life-history of cancer patients, I have found that those who subsequently develop this malady, are even more prone to infectious diseases than the non-cancerous.

Thus, of my 267 female cancer patients, 13 had suffered from small-pox (4·8 per cent.), 16 from typhoid fever (6 per cent.), and 1·1 per cent. from pneumonia ; whereas, of 83 women with non-cancerous tumours, 1·2 per cent. had suffered from small-pox, 6 per cent. from typhoid, and 2 per cent. from pneumonia.

According to Lubarsch, those actually suffering from cancer are seldom attacked by infectious diseases ; thus, among his 569 cancer patients, not a single instance of diphtheria, typhoid fever, acute rheumatism or cerebro-spinal meningitis was noted ; and only 2·4 per cent. of these patients got pneumonia.

Virchow believes that the cancerous are more prone to inflammatory affections, than the non-cancerous.

With regard to rheumatic fever, of my 267 female cancer patients, 24, or 8·9 per cent., had suffered from it; whereas, of 83 women with non-cancerous tumours, 7 had been thus affected, or 8·4 per cent.

### Insanity and Cancer.

The liability of insane persons, imbeciles and idiots to cancer, is decidedly below the average ; and they are generally debilitated and of low vitality. The like is true of prison and workhouse inmates.

With the advent of more complex conditions of existence and greater competition, the tendency to insanity and suicide has undoubtedly increased in all modern communities ; and it is especially among those who have failed in the race, that these maladies are so unduly rampant. Hence, in our own country, their increase has been mainly among the poor ; and men have been affected more than women.

It is beyond all question, that cancer is comparatively infrequent among the inmates of our lunatic asylums, who share this peculiarity with convicts, paupers, savages and monkeys. Imbeciles and idiots seem to be even less susceptible, than other demented persons.

With regard to the inmates of lunatic asylums, the evidence is of a very convincing kind.

Some apposite data bearing on this subject, are contained in the appendix to the Fifty-fifth Report of the Lunacy Commissioners, for the year 1900. Thus, of the 8,356 deaths which occurred during that year, in the institutions under their care, only 186—or 1 in 45—were due to malignant disease. Of these 4,362 were men, of whom 66 died of malignant disease, or 1 in 66; and 3,994 were women, of whom 120 died of malignant disease, or 1 in 33. The average age of the men at death was forty-five years, and of the women fifty-one.

For comparison with these figures, we may refer to the national statistics for the year 1900, which show that among the general population, thirty-five years old and upwards, 1 in 15 men, and 1 in 9 women, eventually died of cancer.

In a valuable essay on this subject by H. Snow,[1] it is shown that of 5,364 adult lunatics, who died while under treatment in the Hanwell and Hitchin Asylums (1870-1891), only 135 died of cancer, or 1 in 39: of these 2,741 were women, of whom 101 died cancerous, or 1 in 27: and 2,623 were men, of whom 34 died cancerous, or 1 in 77.

Of 1,000 insane women in Ontario asylums, submitted to gynæcological examination by Hobbs,[2] only 3 were found to have cancer—the uterus being the part affected in all.

In this connexion it is interesting to note, that such common non-malignant tumours as uterine myomata and ovarian cystomata, are also decidedly rare among the insane, as the researches of Wigglesworth,[3] Urquhart,[4] Hobbs and others conclusively prove.

In marked contrast with the rarity of cancer in insane women, is their great proclivity to tubercle—especially to phthisis; thus, during the year 1900, of 3,994 deaths among English female asylum inmates, no less than 592 were due to phthisis.

### Grief, Anxiety and Mental Distress.

Some authors attach great importance to grief, anxiety and mental distress, as causes of cancer; and they have adduced statistics in support of their belief. With regard to this, I can only say, that the majority of cancer patients whose life-history I have investigated, appeared to me to have been less exposed to depressing influences of this kind, than most women of corresponding age in the general population.

### Prison Inmates etc.

Having seen it stated that cancer is rare in prisons, where but little animal food is allowed and hard work is exacted, I have examined the reports of the commissioners of prisons, to determine the validity of this matter. The data they contain strongly support the contention.

[1] *Journal of Mental Science*, October 1891, p. 548.
[2] *American Journal of Obstetrics*, etc., February, 1902.
[3] *Journal of Mental Science*, January, 1885.
[4] *Edinburgh Medical Journal*, October, 1901, p. 315.

Thus, from the reports for the years 1898 and 1897, it appears that of 5,915 convicts, only 3 died of malignant disease during those years, or 1 in 1,971. These prisoners were of all ages above twenty years, hardly any being under that age. The three deaths from malignant disease all took place among the male convicts, of whom there were 5,547, so that their cancer mortality was 1 in 1,849. Among the 368 female convicts, there was not a single death from malignant disease.

In the general population of the same age and during the same years, the mortality from malignant disease amounted to 1 in 698—for males 1 in 845 and for females 1 in 603.

Thus the mortality from malignant disease in the general population, was nearly thrice as great as that experienced by these convicts.

The prison population is very prone to tubercle, according to Ziemssen, nearly one-half of the total deaths being due to this cause, the pulmonary form of the disease being exceptionally frequent. Their general death-rate is also much above the average, the mortality ratios for heart disease and suicide being exceptionally high.

## Workhouse Inmates etc.

Having gained the impression by visiting workhouses, that cancer is of comparatively rare occurrence among their inmates, I have endeavoured to test the validity of this impression, by reference to such data as are contained in official reports. Notwithstanding the lavishness of the Poor Law administration in this kind of publication, I have found very little satisfactory information available on the subject.

From such crude data as I have gathered, it may be inferred that the inmates of these institutions are less prone to cancer, than persons of corresponding age and sex in the general population.

I am indebted to Mr. J. J. Simpson, Clerk of the Bristol Guardians, for the following particulars: during the years 1901 and 1902, 888 deaths took place among the inmates of the Bristol workhouses, and of these 54—or 1 in 16—were due to cancer. The majority of the defunct were of post-meridian ages, only a few children being included, and males predominated to the extent of about 56 per cent. In the general population for the year 1900, the ratio of cancer deaths to the deaths from all causes, among persons forty-five years old and upwards, was 1 in 11 : during the years 1888-1901, of 6,791 deaths at Guy's Hospital—mostly adults—816 due were to malignant disease, or 1 in 8.

Dr. John R. Lunn, medical superintendent of the Marylebone Workhouse Infirmary (London), kindly furnished me with the subjoined data, as to the prevalence of malignant disease in that institution. The figures are based on the average for the three years 1900-1902. The total deaths amounted to 525 a year, of which 36 were due to cancer, or 1 in 14 : of 270 males 16 died of this malady, or 1 in 17 ; and of 255 females, 20 died of it, or 1 in 13.

In a previous chapter,[1] I have refuted the doctrine of cancer being *morbus miseriæ ;* and have shown its undue prevalence among the well-to-do.

[1] Chapter III.

### Convents etc.

Several Continental authors have reported that cancer is rare in convents, monasteries and similar institutions, where a frugal regimen is enforced; according to Legrain and others, this disease is almost unknown among the Trappist, Carmelite and Carthusian monks, who abstain from flesh food.

### Dermatoses.

I have often noticed on the trunk, face, upper limbs etc., of cancer patients, minute, pink telangiectases; but these are also commonly seen on the non-cancerous of corresponding age and sex. A few years ago these minute spots, with which I have been familiar for the last quarter of a century, were suddenly discovered by certain writers, and boomed as an immense novelty—pathognomonic of cancer. Of course, directly the matter was closely looked into, it was found impossible to maintain these absurd claims; for as Gebele, Raff and Symmers soon showed, these vascular growths are just as common in the non-cancerous, as in the cancerous; and they seem to be a usual concomitant of incipient senescence.

These telangiectases were no doubt in de Morgan's mind, when he referred to "small outgrowths of warty, vascular or dermoid structure," as often being concomitant with cancer.[1]

I have, however, rarely seen warty or dermoid outgrowths in this connexion; nor have I noticed that eczema, psoriasis or other dermatoses, often appear in the course of this disease, as Bazin and Hardy allege. Herpetic manifestations and chronic seborrhœa I have rather more frequently seen.

We are indebted to the dermatologists, and especially to Unna, for recognition in comparatively recent times of a curious morbid condition called *acanthosis nigricans*, which has been found in association with intra-abdominal cancer.[2] The predominant features of this malady are papillary and pigmentary cutaneous dystrophy, together with hair and nail lesions, wasting, cachexia etc. The clinical syndrome has some resemblance to that met with in "Addison's disease," from which, however, it differs in the rough, warty, symmetrical cutaneous patches, wherein the pigmentation concentres, while the buccal membrane is never pigmented. Although abdominal cancer is usually concurrent with this curious morbid condition, cases have been reported in persons quite free from cancer; and, of course, it is only a minority of abdominal cancer cases that are thus complicated.

Hue[3] has reported an instance, in a woman aged forty-five, the subject of cancer of the cervix uteri, with symptoms of dissemination.

[1] "The Origin of Cancer," 1872.

[2] For further particulars reference may be made to Couillaud's essay (*Gaz. des Hôpitaux*, No. 42, 1892, p. 413), and to Unna's book on "The Histopathology of Skin Diseases," 1896.

[3] *Normandie Méd.*, August 15, 1893.

## Paralysed Parts and Cancer.

'It may be stated of feebly vitalized parts in general, that they have but little proclivity to cancer. This is specially true of paralysed, atrophying, and asthenic parts, which hardly ever originate any kind of tumour, as was long ago indicated by Broussais. I have never myself seen a single instance of malignant disease, that had originated under such circumstances; and Sir R. W. Gowers, with his large experience of paralytic affections, in answer to my inquiry, says that he has never seen malignant disease originate in paralysed parts. Since most paralysed parts appertain to the extremities, which are but little prone to originate malignant disease, this proclivity might at first sight, be thought sufficient to explain the immunity. I find, however, that about 2 per cent. of all malignant tumours in males, and 1 per cent. in females, originate from the extremities; which is a much greater proportion than is met with in the paralytic, as is evidenced by the almost complete absence of records of cases of malignant disease of paralysed parts. I think there can be no doubt that this immunity of paralysed parts from cancer, is due to enfeebled vitality, rather than to loss of hypothetical neuro-trophic influence, for reasons I shall have occasion to indicate in a subsequent chapter.[1]

The only instances of cancer originating in paralysed parts known to me, are two or three cases cited by Cruveilhier[2] of women who, having had the spinal cord completely or almost completely destroyed in early life, with consequent wasting of the lower limbs etc., nevertheless, developed fatal cancer of the uterus, at the usual age.

A case of cancer arising from a perforating ulcer of the foot, has been reported by Zahn.[3]

## Menstruation.

Ever since Broussais wrote, "Les règles douloureux annoncent un foyer d'irritation dans le col utérin, et le cancer de cette partie en est souvent la suite à l'époque qu'on appelle critique, quand on n'a pas calmé l'irritation longtemps avant cette époque," attempts have been made to ascribe the great frequency of cancer of the female reproductive organs to catamenial derangements.

In this connexion, I have ascertained the following facts :—

Of 100 uterine-cancer patients under my observation, the disease was first noticed :

| | |
|---|---|
| Before the menopause | in 50 |
| About the time of the menopause | ,, 21 |
| After the menopause | ,, 29 |

In these patients, the mean age at the first appearance of menstruation was 14·5 years, and at its cessation 46 years.

The longest interval between the menopause, and the onset of the disease, was 27 years.

[1] Chapter XVIII. [2] *Anat. path.*, t. ii., liv. 28.
[3] *Arch. f. path. Anat.*, 1889, Bd. cxvii., S. 39.

Of 104 of these patients, menstruation had been normal in 96; and irregular only in 8 (scanty 6, profuse 2).

Of 1,232 patients with cancer of the cervix uteri, Andriezen and Leitch found that only 71, or 5·8 per cent., had suffered from catamenial irregularity.

Of 87 females comprised in my list with mammary cancer, the disease was first noticed:

| | |
|---|---|
| Before the cessation of menstruation .. .. .. .. | in 35 |
| At about the time of the menopause .. .. .. .. | „ 10 |
| After the cessation of menstruation .. .. .. .. | „ 42 |

In these patients the catamenia first appeared at 14·5 years, and ceased at 46·3 years.

The following table from Paget [1] shows the ages at which menstruation ceased in 400 women, and the ages at which cancer of the breast was first detected in an equal number:—

| Ages. | Cessation of Menstruation. | Onset of Cancer. |
|---|---|---|
| Below 35 .. .. | 9 | 36 |
| 35 to 40 .. .. | 51 | 62 |
| 40 „ 45 .. .. | 140 | 78 |
| 45 „ 50 .. .. | 159 | 101 |
| Above 50 .. .. | 41 | 123 |
| | 400 | 400 |

The only catamenial abnormalities noticed in my 87 breast-cancer patients were, profuseness in 6, irregularity and scantiness in 4.

These facts suffice to show that, even in uterine and mammary cancer patients, the normality of the catamenial function is seldom disturbed; that it begins earlier and ceases later in them, than in the generality of women, is simply an indication of the more vigorous sexual life of cancer patients, which accords with other facts ascertained by me, relative to their life-history, such as high fertility, early marriage etc.

Of like import is the fact, that the age incidence of mammary cancer is very similar in both sexes, as I have elsewhere shown.[2]

With regard to gastric cancer, as Brinton [3] long ago pointed out, the very similar age incidence of the malady in both sexes, shows that no specific influence attaches to menstruation in this connexion.

It is thus evident that the catamenial function *per se*, has no causal connexion with the development of cancer.

## Alimentation.

In the course of this work I have, on many occasions, indicated the important part played by the conditions of existence, in determining the incidence of cancer. Among these conditions alimentation is an important factor.

In the present imperfect state of our knowledge, it is singularly

[1] "Lectures on Surgical Pathology," 1853, vol. ii., p. 327.
[2] "Diseases of the Breast," 1894, p. 244.
[3] "Diseases of the Stomach," 1864, p. 225.

difficult to determine the precise effect of diet in this direction, in any particular case; because, in all probability, its influence becomes appreciable only very slowly, or after more than a single generation of individuals has been exposed to it. Hence the failure of the praiseworthy attempt, of the British Medical Association's collective investigation committee[1] to solve this problem. From returns collected by this committee, it appears that of 194 cancer patients, 123 had been moderate eaters, 59 small eaters, and 12 large eaters. With regard to meat, 99 had been moderate, 78 small, and 16 large eaters. There was not a single strict vegetarian among them; and, only a few, had a bias to vegetarianism.

In this connexion, it may be well to recall the fact, that although cancer is remarkably rare in vegetarian communities, yet complete exemption cannot be claimed for such; and the like is true of herbivorous, as compared with carnivorous animals. In spite of these facts, which indeed are only such as might have been expected from the essential nature of the problem, there cannot be the slightest doubt—in face of the overwhelming evidence I have adduced in the course of this work—that the incidence of cancer is largely conditioned by nutrition.

## Salt.

The presence of salt in animal tissues is so universal, that it may be regarded as indispensable to their constitution, functional integrity, and nutrition; but, in general, flesh-eating animals find a sufficient supply of it, in the alimentary substances on which they subsist, and they dislike any artificial addition thereto. It is in herbivora, that the craving for additional salt is so common. Similarly with mankind, it is among the vegetarians that the salt consumption *ab extra* is greatest; and Bunge regards the continued use of vegetable foods, as being the cause of the demand for salt as a condiment. This relationship was long ago indicated by Darwin,[2] who says of the South American people: "The Indians eat much salt, their children sucking it like sugar. This habit is very different from that of the Spanish Gauchos (great meat eaters) who, leading the same kind of life, eat scarcely any salt. According to Mungo Park, it is people who live on vegetable food, who have an unquenchable desire for salt."

Cancer is commoner in Argentina—which comprises the pampas region inhabited by the Gauchos, who for months subsist entirely on beef, and never touch salt—than in other parts of South America. On the other hand, among the natives of Egypt, who are of vegetarian habits, and consume immense quantities of salt, cancer is almost unknown, as I have shown in a previous chapter.[3]

In like manner with our domesticated animals, cancer is of most frequent occurrence among dogs, which are carnivorous, but avoid artificially salted food; and cancer is also common among cats, which have similar habits.

[1] *British Medical Journal*, February 26, 1887.
[2] *Naturalist's Journal of Researches*, etc., 1891, p. 139.
[3] Chapter II.

Considerations of this kind, which may easily be multiplied, seem to me to contra-indicate Braithwaite's theory,[1] that an excess of salt in the diet is a factor in the causation of cancer.

### Alcohol.

Meat-eating communities are, as a rule, also alcohol-consuming. There is, however, no evidence to show that the habitual consumption of alcoholic liquors *per se*, in any way predisposes to cancer.

No doubt the last half-century has witnessed great increase in alcoholism and intemperance; and indulgence of this kind has now certainly attained harmful proportions. But, because this access of intemperance has coincided with augmented cancer mortality, it does not necessarily follow that this is a legitimate basis for inferring ætiological connexity; and, against any such conclusion, I would urge the following considerations:—

1. As the result of special inquiries into the life-history of female cancer patients, based upon the analysis of several hundred cases, I have shown that these persons had almost invariably led regular, sober and industrious lives;[2] and Butlin's collective investigation report,[3] on women with mammary cancer, is of similar import.

2. With regard to male cancer patients, Isambard Owen[4] has shown that of 116—aged from forty to sixty-five—who had died of malignant disease, 50·76 per cent. had been total abstainers or habitually temperate, 25·7 per cent. had been "careless" drinkers, and 22·3 per cent. had been decidedly intemperate. Newsholme,[5] however, concludes that, among men, the cancer mortality for abstainers per 1,000, is 0·95, and for non-abstainers 1·32; but, as he points out, not much reliance is to be placed in these results, owing to paucity of data and other sources of fallacy.

3. It accords with the foregoing conclusion, that the increase in alcoholism has been greater among women, than among men; whereas, with the increased cancer mortality, it is just the converse.

4. It has been noticed that hotel-, restaurant- and inn-keepers, brewers and commercial travellers, who have special facilities for obtaining alcoholic drinks, have a high cancer mortality: but, that this is due to some other cause than alcoholism, is evident from the fact that printers, compositors, pressmen, paper-makers, iron and steel workers—who are notorious for their drunken habits—are, however, less prone to cancer than any other workers in the whole community.

5. In Bavaria and Saxony, the cancer mortality is very high; and Wolff ascribes this to the beer-drinking habits of the natives; but, as against this, I should point out that in Norway, Sweden and Denmark, where the consumption of alcoholic liquor is small owing to restrictive legislation, the cancer mortality is even higher than in Bavaria and Saxony. Similarly with regard to wine-drinking countries, it is only

[1] *Lancet*, December 7, 1901.
[2] Middlesex Hospital Surgical Report for 1888 (by the author).
[3] *British Medical Journal*, February 26, 1887, p. 59.
[4] *Ibid.*, January 23, 1888. [5] *British Medical Journal*, 1903, vol. ii., p. 1529.

necessary to recall the great rarity of cancer among the inhabitants of the Mediterranean littoral, Spain and Italy, where wine-drinking is uinversal, to realize that this custom has nothing to do with the incidence of cancer. Of similar import is the rarity of cancer among the whisky-drinking peasants of the "wild west" of Ireland. Examples of this kind, which might easily be multiplied, suffice to show that neither beer, wine nor spirit drinking, entails proclivity to cancer.

6. Of like significance is the fact, that while alcoholism is at its maximum in the slums of our large towns, it is just in these localities, that the cancer mortality is the lowest.

From the ensemble of these indications we may safely conclude, that persons addicted to alcoholism—whether in the form of beer, wine or spirit—have no special proclivity to malignant tumours.

### Water.

If it were true, that "evidence produces conviction as much by the frequency of its repetition as by its weight," then we should be obliged to believe that cancer is often spread through the agency of drinking-water.

Even as long ago as 1809, it was alleged by William Lambe,[1] that all drinking-water was contaminated by arsenic, which caused those who drank it to become cancerous; hence, he advocated the use of arsenic-free distilled water for the cure of cancer, and he narrates in detail many striking "cures" effected in this way.

It was probably owing to the prevalence of ideas of this kind, that such strenuous opposition was manifested to the New River Company; when, in the early part of the nineteenth century, it substituted iron pipes for the bored elm-trunks, that had previously been used for conveying drinking-water to London; the opposition gravely alleging—as we learn from a correspondent in the *Standard*[2]—that the consumption of water conveyed through iron pipes would produce cancer.

Recently, the prevalence of cancer in the volcanic plateau, which constitutes the Ballarat gold-field, has been ascribed by J. H. Webb,[3] to the drinking of rain-water, that had been stored in galvanized iron or cement-lined tanks etc.

In like manner, it has lately been suggested by J. Hutchinson, that cancer is caused by arsenic-contaminated beer.

In such instances as the foregoing, the incriminated element generally is, a small quantity of arsenic dissolved in the water. With regard to this, it may be stated that in Styria, where arsenic eating is said to prevail, the cancer mortality is by no means high; and, in this country, among those engaged in industrial occupations involving contact with arsenic, no undue cancer mortality has been noted. In short, there seems to be no sufficient basis for the belief, that the ingestion of arsenic is a cause of cancer.

In other instances, water has been alleged to cause cancer, through

[1] Reports, etc., on the Effect of a Peculiar Regimen on Cancer, London, 1809.
[2] J. W. Ford in the *Standard* of May 1, 1899.
[3] *Lancet*, 1901, vol. ii., p. 976.

its harbouring micro-organisms or other organic impurities (Arnaudet, Behla etc.); but these allegations have never been substantiated.

Equally destitute of foundation are the assertions that cancer is caused by the softness or hardness of drinking-water, by its contamination with sewage etc.; and the claims of curative properties for hard, soft, and various mineral waters, are just as unsubstantiated.

In short, I have failed to find any valid evidence, that the incidence of cancer is in any way dependent upon the supply of drinking-water.

### Late Marriage, Decline in the Birth-Rate, Celibacy etc.

Under favourable conditions, the population of a country has been known to double itself—independently of immigration—in twenty-five years or less; but, in modern communities, such a rate of increase is now never met with, and, in our own country, the last doubling of the population has taken nearly sixty years. It is thus obvious that, in all modern communities, the reproductive capacity is enormously repressed. Moreover, this repression is much greater among the wealthy and well-to-do classes, than among the rest of the community, as Bertillon has shown; thus, while the birth-rate per 1,000 women of the London population—aged fifteen to fifty—for the rich was only 75, the corresponding figure for the poor was 143.[1] In all modern occidental communities, there has been a marked decline in the birth-rate, during the last half-century, which is still in progress; and this, of course, implies late marriages, with lessening fertility thereof, and increasing celibacy.

Social scientists have been much exercised to explain this greatly diminished fertility of wealthy modern communities, and the general tendency has been to ascribe it to the wholesale adoption of "positive" checks; but, it seems to me much more likely that most of it is due to quite other causes, viz., to a diet unduly rich in proteids. In the organic world in general, it has been clearly proved that an abundant supply of nutriment everywhere causes great diminution of gamogenetic fertility; X
and, in our country, as I have indicated, the falling off in this respect has been chiefly among the well-to-do. This explanation of the diminished fertility of well-to-do communities, was long ago advanced by Doubleday;[2] and it finds a certain amount of support in experiments on animals, for rats fed on meat diet have been found to experience great diminution in their reproductive capacity and fertility. It is not improbable, therefore, that diet plays an important part in the increase of cancer, the decrease of tubercle and the diminution of the birth-rate.

As I have elsewhere indicated,[3] the increase of cancer among women cannot be ascribed to their fecundity; for, in addition to the facts there adduced, it may also be mentioned, that while the marriage-rate has of late increased, the birth-rate has markedly declined; so that the fecundity of modern women has diminished, while their proclivity to cancer has increased.

[1] For further details, *vide* Chapter II., p. 26.
[2] Doubleday's important discovery was rejected by John S. Mill, who was, however, more of a logician and metaphysician than a biologist or social scientist; indeed, Mill's lack of biological knowledge is painfully apparent in all his works.
[3] Chapter XI.

Of course, such changes in social conditions as those with which we are here concerned, have been attended with concurrent alterations in the age constitution of the population, with survival of greater numbers to the cancer age; but, only a very small part of the increased cancer mortality—which has been estimated at $\frac{1}{40}$—can be thus accounted for.

## Occupation etc.

Although it cannot be said that persons of any rank or station in life are exempt from cancer; there are, nevertheless, some remarkable differences in the incidence of the disease, among the various social strata. I have already had occasion to point out the much greater prevalence of cancer among the well-to-do, and among the agricultural community, than among the less prosperous of the industrial classes in our great towns, as well as its comparative rarity among paupers, lunatics, and the prison population.

Perhaps the most significant result hitherto attained by statistical investigation of this subject, is that arrived at by Dr. Tatham,[1] who found that the mortality from cancer during the decennium 1881-1890, was more than twice as great among well-to-do men having no specific occupation, as among occupied males in general, the respective cancer mortality ratios being 96 for the former and only 44 for the latter.

In like manner, Aschoff has shown that, in the Berlin population, cancer was of most frequent occurrence among persons of independent means, living on their income or pension.

All statistics show that printers, compositors and pressmen experience a very low cancer mortality, while their death-rate from tubercle and their general mortality, are both very much in excess of the average; and this class is notoriously one of the most intemperate as regards alcohol etc., in all modern communities.

According to the Twelfth United States Census Report, for the year 1900, the cancer death-rate for this class was 22 per 100,000 living, the corresponding figure for pulmonary tubercle being 435.

Another class of workers but little prone to cancer, are the miners—especially coal-miners—and quarrymen; the United States statistics for this class show a cancer death-rate of 33; and a phthisis death-rate of 120.

Aschoff's Berlin data, place the miners next to the printers, in respect to comparative immunity from cancer.

In England, there are few districts where cancer is less prevalent, than in the great colliery centres of Derbyshire, South Wales, Durham and Lancashire; and in the mining and quarrying districts of Cornwall, North Wales and elsewhere, very low cancer death-rates also prevail.

With regard to the very high mortality of chimney-sweeps from cancer, as shown by the English national statistics, I am inclined to think that the calculation is based on too small a number of cases to give a reliable average, and is otherwise defective; at any rate, nothing of the kind has been noted in the United States, nor in Continental European countries.

[1] Supplement to Registrar-General's Fifty-fifth Annual Report, 1897.

Moreover, I have found that cancer of the corresponding anatomical part in women—the vulva—is nearly as common as cancer of the scrotum in males: for, of 4,628 primary cancers in females, 104 were of the vulva or 2·2 per cent.; while of 2,669 cancers in males, 76 were of the scrotum or 2·8 per cent.

In general, cancer is comparatively infrequent among the working classes of our large towns, especially in the great industrial centres, and among the cotton and textile operatives, iron and steel workers etc.

On the other hand, among the well-to-do, the cancer mortality is certainly much in excess of the average.

Thus, among the leisured and professional classes, the United States Census Report—for 1900—shows that high cancer death-rates prevail, especially for the clergy, merchants, brewers, hotel and restaurant keepers, hotel servants, butchers, agriculturalists, sailors, commercial travellers, carpenters etc.

Workers in soot, tar, paraffin, arsenic etc., are specially prone to certain forms of cutaneous cancer; and it has been reported, that those employed in particular cobalt and nickel mines, are prone to quasi-malignant pulmonary disease.

There are good reasons for believing that farm labourers, gardeners, sailors, and those who follow out-of-door occupations, are unduly prone to cancer of the lower lip.

Of 36 men with cancer of the lower lip who came under my observation in London hospital work, 5 were farm labourers, 5 general labourers, 3 sailors, 2 bricklayers, and 1 each as follows:—saddler, cowman, blacksmith, stoker, worker in a paper factory, piano-maker, sewerman, bailiff, gardener, brazier, carpenter, gas-fitter, costermonger, carman, commercial agent, boatman, waiter, soldier, fireman and groom.

The large proportion of patients engaged in out-of-door occupations comprised in this list, is very remarkable; especially when regard is had to the sedentary occupations followed by the great bulk of the London population, whence these cases were drawn.

With regard to the influence of occupation on the liability of women to malignant disease, perhaps the most significant item hitherto elicited is that brought out by the United States Census Report for 1900, which shows that domestic servants are unduly prone to cancer; thus, during the age-period forty-five to sixty-five, their mortality from this cause was double the average; and, at ages above sixty-five, it was triple the average. Cancer death-rates, above the average, were also noted among nurses, midwives and school-teachers.

With regard to the female hospital patients with cancer, under my observation, most of them had been supported entirely by their husbands' earnings; but such of them as had worked for their living—whether married, widowed or single—had followed the following occupations in 142 cases:—thus, domestic service 62 (cook 17, charwoman 13, housekeeper 6, other forms of domestic service 26); needlework, dressmaking etc. 28; sick nurse or midwife 16; laundry 16; governess or school-teacher 7; factory 7; shop assistant 4; barmaid and actress, of each 1.

## CHAPTER XVII

### FAMILY HISTORY

The problem of heredity, in relation to disease, has hitherto seldom been viewed in a right light. The fundamental error has been the tacit assumption that pathological states, like normal conditions, are almost invariably inherited. It has been overlooked that the predispositions of the organism are to normality; and that diseases—like other recently acquired characters—tend to disappear under suitable environmental conditions. In fact, so great is the preponderating influence of the previous ancestral balance, that diseases are never reproduced in the offspring, with the same constancy and regularity that normal conditions are. Hence, even in families where hereditary morbid tendencies are the strongest, most of the members usually escape; and this is notably the case with cancer.

Nevertheless, it is undoubtedly true that the descendants of a family in which a new morbid variation has appeared are, other things being equal, more likely to vary again in a similar way, than are persons whose relatives have never manifested such variation. This principle, as I shall proceed to show, is also applicable to cancer.

Thus, in Broca's celebrated case of multiple family cancer to be presently cited, of the twenty-six descendants of Madame Z. who attained or exceeded the age of thirty, fifteen died of cancer; whereas the cancer proclivity for the same number of persons of the general population at the corresponding period of life, is considerably less than one; that is to say, the liability to the disease was here increased more than fifteen times by the influence of heredity.

No doubt it is a difficult thing to define scientifically, the precise nature of the essential basis on which pathological heredity depends; but, for present purposes, it will suffice if we adopt Hughlings Jackson's conception: "To similar causes there are in those similarly constituted—like members of families—similar modes of physiological and pathological reaction." If we knew more about the circumstances under which predisposition to cancer arises, the problem of prevention would be simplified; for then we might be able to determine how—by cross breeding or otherwise—to convert morbidly-tending into healthy stocks. What, then, is the predisposition most likely in breeding, to counteract a tendency to cancer? To this it may be answered, according to my belief, that persons of a spare physical type, of medium weight and height, active disposition, fond of open-air life and exercise, and getting plenty of it, with well-developed sexual system, and concomitant frugality of habits—especially in respect to food—and above all, free from any cancerous or tuberculous predisposition and proclivity to obesity; such are, I think, the types most likely in breeding, to counteract a tendency to cancer.

According to Hippocrates, to prevent the diseases to which individuals are hereditarily predisposed, we ought to change their constitution; and this is to be effected, by bringing them up under different conditions of existence, from those in which their parents have lived. In the preventive treatment of cancer, this indication should not be neglected.

In referring to this matter Darwin says: "The increased vigour resulting from cross-fertilization, is allied, in the closest manner, to the advantage gained by change of conditions. So strongly is this the case, that in some instances cross-fertilization gives no advantage to the offspring, unless the parents have lived under slightly different conditions. So that the really important thing is, not that two individuals of different blood shall unite, but two individuals who have been subjected to different conditions."

Very conflicting are the views now prevalent as to the hereditability of the disease. These contradictory opinions are no doubt largely attributable, to the prevailing confusion in the fundamental conceptions of heredity. As I cannot here enter on the burning question of Weismannism *versus* Darwinism, it must suffice for me to state; that I regard the distinction between somatic and germ cells, on which Weismann's theory is based, as artificial. As I have previously indicated, the reproductive properties manifested by somatic and germ cells are the same in kind, and they differ only in degree. I also believe that acquired characters are hereditable. In weighing this question, Weismann has ignored the evidence derived from the study of disease, which is incompatible with his theory and conclusions, as the facts to be cited in this chapter alone suffice to show.

The first principles being in this unsettled state, it will be well to pass at once to the consideration of the cardinal facts.

As Karl Pearson has remarked: "It is difficult to conceive that longevity and general health can be inherited, if the tendencies to particular diseases do not run in families."[1]

To my mind, the hereditability of cancer is more conclusively proved, by the occurrence of several instances of the disease in certain families, in one or in successive generations, than by any other consideration.

Although such coincidences may not invariably amount to absolute proof of hereditary transmission; yet, when we see families thus affected, in which tumours of this kind develop in the same organs, and that during several generations, it seems to me unscientific to deny the hereditability

[1] As an example of this, reference may be made to the transmission of deaf-mutism. Buxton's researches show that of 303 marriages, in which both of the contracting parties were deaf and dumb, one in twenty of the offspring were similarly affected; and that of 310 deaf-mutes married to hearing people, the proportion of deaf and dumb among the offspring was 1 in 135. In the general population at this period the proportion of deaf-mutes was about 1 in 1,600. Independent investigations since carried out by Mygge, Hartmann and others have fully confirmed Buxton's results.

of the disease, especially when, as is frequently the case, these morbid manifestations are exclusively confined to one side of the family or to one sex.

Such cases show that there is inherited a special abnormality of organs, tissues, and cells, which manifests itself in their aptness to beget cancer. To account for this we may suppose that, just as an inherited capacity for a certain regularity and amount of growth, is a quality inherent to all normally evolving cells ; so irregularity of growth may also become hereditable, in cells that have once acquired the habit of aberrant propensities. In the one case, as in the other, it is to the persistence of impressions in the living protoplasm, that we must look for the explanation of this phenomenon. Hence, when we speak of hereditary transmission in these cases, what is meant is, that such abnormalities of growth are but the manifestations of long antecedent physical impressions. "It appears to me almost certain," says Darwin, "that the characters of the parents are 'photographed' on the child, by means of material atoms derived from each cell of both parents, and developed in the child."

The problem of heredity is, in fact, the problem of the manner of distribution of characters among the germ-cells.

Such instances of multiple family cancer, as the subjoined, prove the hereditability of the disease ; for, it is obviously impossible that those thus affected could have acquired the malady from a common source of infection, and concurrences of this kind cannot be interpreted as being fortuitous.

## Breast.

1. The following case recorded by Broca,[1] is the most complete of its kind that has ever been published ; and this is mainly due to the fact, that the family included an eminent physician among its members, who furnished the particulars as under :

*First Generation.*—Madame Z. died of cancer of the breast, aged sixty. She left four daughters—A, B, C and D.

*Second Generation.*—The four daughters of Madame Z.—

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (1) | Madame | A | died | of cancer | of | liver, | aged | 62. |
| (2) | ,, | B | ,, | ,, | | ,, | ,, | 43. |
| (3) | ,, | C | ,, | ,, | | breast | ,, | 51. |
| (4) | ,, | D | ,, | ,, | | ,, | ,, | 54. |

*Third Generation.*—Madame A. had three unmarried daughters, still alive and well, aged sixty-eight, seventy-two, and seventy-eight years.

Madame B. had five daughters and two sons. First son died—not cancerous—at the age of twenty-eight, and without issue. Second son died of cancer of stomach, aged fifty-four, and without issue.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| First | daughter | died | of cancer | of | breast, | aged | 35 | |
| Second | ,, | ,, | ,, | ,, | ,, | ,, | 35 to 45 | All unmarried, and without issue. |
| Third | ,, | ,, | ,, | ,, | ,, | ,, | 35 to 45 | |
| Fourth | ,, | ,, | ,, | ,, | liver, | ,, | 35 to 45 | |
| Fifth | ,, | ,, | not cancerous, | | | ,, | 60 | Married, but no issue. |

[1] "Traité des Tumeurs," 1866, t. i., p. 151.

Madame C. had five daughters and two sons :

| | |
|---|---|
| First son died in the army without issue. | |
| Second son alive and well, aged 72. | He had a son who died paraplegic, aged 18, and an only daughter, who is alive and well, aged 24, unmarried. |
| First daughter died of cancer of the breast, aged 37, leaving two sons and three daughters. | First son, aged 58, alive and well. He has three sons alive and well, the oldest aged 30.<br>Second son died young, abroad, without issue.<br>First daughter died in child-bed, aged about 28.<br>Second daughter died of cancer of the breast, aged 49. She left two daughters. Both are alive and well; the elder is 22.<br>Third daughter died of phthisis, aged 41. |
| Second daughter died, aged 40, of cancer of the breast. | She left an only son, who is alive and well. |
| Third daughter died, aged 47, of cancer of uterus. | Unmarried. |
| Fourth daughter died, aged 55, of cancer of the breast. | She left two sons, who are alive and well. |
| Fifth daughter died, aged 61, of cancer of liver. | Unmarried. |

Madame D. had an only son, who is alive and well, aged seventy.

2. In a family known to Sibley,[1] the mother and her five daughters all died of cancer of the *left* breast.

3. Velpeau [2] met with cancer of the breast, in a mother and her three daughters.

4. Korteweg [3] has seen the same malady in grandmother, mother and daughter.

5. Gibson [4] met with it in four sisters; and Moore [5] also knew of a family, in which all the sisters had cancer of the breast.

6. Of 14 members of 2 related families known to Iterson,[6] 8 certainly died of cancer (5 of the female breast), and 3 others probably.

7. A woman, aged thirty-seven, came under my observation with cancer of the breast, who had lost two sisters also from cancer of the breast, and a brother who died, aged thirty, of " tumour of the back." This patient's father died, aged forty-two, of cancer of the breast; and of his two sisters, one died, aged fifty-two, of cancer of the breast, and the other of cancer of the liver.

8. J. H. Power [7] has reported the case of a man, whose right breast had been amputated for cancer, with subsequent recurrence in the axilla, whose father died of cancer of the right breast. Of this patient's two brothers and eight sisters, all but two of the latter—who died young—were the victims of cancer. Of his brothers, the elder died of " cancer of the

[1] Transactions of the Medico-Chirurgical Society of London, 1859, vol. xlii., p. 110.
[2] " Traité des maladies du sein," 1858, p. 685.
[3] " Veröffentlichungen des Comitees für Krebsforschung," 1902.
[4] Cited by S. D. Gross in his " System of Surgery," 1882, 6th edit., vol. i., p. 242.
[5] " Antecedents of Cancer," 1865, p. 16.
[6] Veröffentlichungen des Comitees für Krebsforschung," 1902.
[7] *British Medical Journal*, 1898, vol. ii., p. 154.

throat," and the younger of cancer of the left axilla. Of his sisters, four have died of cancer of the breast; and the two now living are both suffering from the same disease, also of the breast.

9. There is in the museum of the Middlesex Hospital,[1] a specimen of sarcoma of the breast, removed from a lady whose two sisters had similar disease—also of the breast; and Paget[2] has cited the case of a lady, the victim of mammary scirrhus (other members of her family were also believed to have died of "cancer"), whose three daughters all developed adeno-sarcoma of the breast.

### Uterus.

1. I have known a woman, aged fifty-three, with uterine cancer, whose maternal grandmother, mother (aged forty-five), mother's sister; and the patient's two sisters (aged thirty-two and thirty-six), had all died of cancer of the uterus. She was one of a family of eleven; of her other brothers and sisters three died in infancy, and five were still alive and well.

2. Atthill[3] mentions the case of a woman, aged twenty-eight, with uterine cancer, whose mother and two sisters also died of cancer of the same organ.

3. Guthmann[4] has met with cancer of the corpus uteri in three sisters; Veit[5] with cancer of the cervix uteri in two sisters; and Cullen[6] with cancer of the uterus in three sisters.

4. Paget[7] has reported an instance of uterine cancer in grandmother, mother and daughter.

5. Péan[8] met with an instance of uterine sarcoma in a child two years old, whose mother died—aged thirty-eight—of malignant disease of the uterus, her mother having also died of the same affection—aged thirty-two.

6. Woods Hutchinson[9] refers to the family history of a lady medical student whose grandmother, mother, two maternal aunts and two sisters, all died of cancer—the uterus being the part affected in four of these relatives, and the breast in two.

### Gastro-Intestinal.

1. Of the celebrated Bonaparte family, Napoleon I., his father, his brother Lucien, and two of his sisters (Pauline and Caroline), all died of cancer of the stomach.

[1] Pathological Catalogue, Nos. 2,079 and 2,093.
[2] "Lectures on Surgical Pathology," 1854, vol. ii., p. 260.
[3] "Clinical Lectures on Diseases of Women," 1876, p. 251.
[4] "Über den Einfluss der Erblichkeit auf die Entstehung des Uteruscarcinoms," Inaug. Diss., Würzburg, 1888.
[5] "Veröffentlichungen des Comitees für Krebsforschung," 1902.
[6] "Cancer of Uterus," 1901, p. 648.
[7] Cited by Moore, "Antecedents of Cancer," p. 16.
[8] "Tumeurs de l'Abdomen," 1895.
[9] "Human and Comparative Pathology," 1901, p. 206.

2. Twenty-three families known to Manichon,[1] comprised between them sixty-nine cancerous members; and of these the stomach was the seat of the disease in no less than fifty-seven. In the part of the country where these families lived, consanguineous marriages were frequent.

3. A woman under my observation, with cancer of the rectum, had lost a sister from the same disease, which had also caused the death of her mother's sister, while the patient's mother died of cancer of the stomach.

4. Höllander knew of a family of which five members had died of intestinal cancer; Childe[2] met with cancer of the rectum in three sisters; Korteweg[3] with cancer of the same part in two sisters; and, according to Lebert, the celebrated physician Broussais and his son, both died of rectal cancer.

5. In Kompe's[4] case, father and son both died of cancer of the colon; the father's father died of malignant disease of the cervical spine; the mother died of cancer of the uterus, and her mother of cancer of the breast.

### External Genitalia.

1. In a man with cancer of the penis known to Warren,[5] the father, grandfather and great-grandfather, had all died of the same malady of the same part.

2. Earle[6] had a patient, with epithelioma of the scrotum, whose grandfather, father and brother, had all died of the same disease.

### Eye.

1. The occurrence has been reported of *melanotic* sarcoma of the *choroid* of the *left* eye, in mother and daughter. The mother, when pregnant with the daughter, who twenty-one years later developed the same disease, was then herself affected in the same way. Mother and daughter had each the diseased eye removed at the Royal London Ophthalmic Hospital, where careful records were kept. Each tumour was found to have originated from precisely the same part of the choroid; and the microscopical structure of each was identical—round and spindle-celled melanotic sarcoma.

In this family it seems almost certain that other of the mother's relatives were similarly affected, viz., her father and her twin sisters, each of whom had lost an eye by extirpation for disease.

A report of this case was first published by Lawford and Collins;[7] and many years afterwards Silcock[8] gave another account of the same. As there are discrepancies in the two reports, as to the presumed nature of the malady which caused the mother's relatives to lose each an eye, the

[1] *Thèse de Paris*, 1896, No. 415.
[2] *British Medical Journal*, 1905, vol. ii., p. 804.
[3] *Op. cit.* [4] Inaug. Diss. Münch., 1883.
[5] Cited by S. D. Gross in his "System of Surgery," 1882, vol. i., p. 242.
[6] Transactions of the Medico-Chirurgical Society, London, vol. xii., p. 305.
[7] Royal London Ophthalmic Hospital Reports, vol. vii., p. 389.
[8] Transactions of the Pathological Society, London, 1892, vol. xliii., p. 140.

foregoing account is of the nature of a compromise, such as seemed most probable after careful study of both of them.

2. An example of malignant disease of the eyeball, in four brothers and sisters, is cited by Otto.[1]

### Glioma.

Many remarkable instances of hereditary glioma have been recorded.

1. Thus, in Newton's case,[2] of a family of 16 children, 10 had died of retinal glioma—the disease being bilateral in 7 cases. Of these 10 children, only 1 lived beyond the age of three years, he had been operated on for unilateral glioma, at the age of three years, and died, aged five years, with recurrence. Of the affected children, 5 were males and 5 females. With regard to the other members of this family, 2 died shortly after birth of bronchitis; and 4 were still alive and well. One of the father's brothers is believed to have died in infancy, from the same malady; but both parents were alive and well.

2. H. Wilson [3] has seen eight children of one family similarly affected.

3. Other instances in which several members of the same family have been affected with glioma, have been reported by Snell,[4] Fuchs, Calderini, Graefe, Sichel etc.

4. Of the children of two brothers known to Feinstein,[5] three of the first family and one of the second, had succumbed of glioma retinæ.

### Miscellaneous Examples.

Many other examples of multiple hereditary cancer may be found in the records of medical science: I subscribe references of several such, *e.g.*, by Roper[6] (of a family of 7, 6 died of cancer—in females the breast being the part affected); Cotoni [7] (6 cases of cancer in the same family); Warren [8] (6 cases of cancer in 3 generations of the same family—in all but one the breast being the part affected); Strümpell (2 brothers with sarcoma of the left kidney); Holländer (of the 31 relatives and descendants of a pair—both of whom died of cancer—16 certainly died of the same disease and probably 3 others); Sprengel (a woman with cancer of the breast, whose brother, father and 2 other members of the family, died of cancer of the liver) etc.

### Cancer and other Tumours in Twins.

Some years ago, Galton [9] published a most instructive study of the life-history of twins, with the object of determining the relative influence between the effects of tendencies received at birth, and those imposed by the circumstances of their lives. He found that many homologous twins

[1] "Pathological Anatomy," 1831, p. 16 (South's translation).
[2] *Australian Medical Gazette*, May, 1902, p. 236.
[3] Transactions of the Pathological Society, Dublin, 1871-1874, p. 108.
[4] *British Medical Journal*, 1905, vol. ii., p. 132; also *ibid.*, 1904, vol. i., p. 1429.
[5] *Rev. des Sci. Méd.*, 1896, No. 93, p. 301.
[6] *British Medical Journal*, 1887.
[7] *Normandie Méd.*, October 1, 1893.
[8] "Surgical Observations on Tumours," p. 281.
[9] *Journal of the Anthropological Institute*, 1876, vol. v., p. 391.

suffered from identical maladies, among which were instances of hernia, flexures of the digits, baldness etc.[1] Carbonell met with identical multiple malformations in twin brothers; and Windle has instanced other cases of identical malformations in twins. The conclusion Galton arrived at, as the outcome of his investigation was, that nature was far stronger than nurture: " We are too apt to look upon illness and death as capricious events, whereas the fact of the maladies of two twins being continually alike, shows that illness and death are necessary incidents in a regular series of constitutional changes beginning at birth, upon which external circumstances have, on the whole, very small effect."

No examples of tumour are comprised among Galton's cases; but, since then, several instances of this kind have been described.

Of these, one of the most remarkable, is the Lawford-Collins-Silcock case, in which twin sisters each had the left eye removed for pigmented sarcoma of the choroid, as previously described; and other instances of " cancer " in twins have been recorded by Bautista Claveria, Gaylord and Wilder.

Peacock has seen Hodgkin's disease in twin boys, four years old; Anseaux identical goitrous tumours in twin brothers; Ahlfeld, congenital hydrocele, on the right side, in male twins; and Leared, ovarian cystoma in twin sisters. Conner met with pigment staining—which is often a pre-cancerous lesion—of the lip and mouth, in twins.

These cases alone suffice to show, that there is an inherited element in cancer and tumour growth.

### In Animals.

Some remarkable examples of the hereditary transmission of melanosis in horses are cited by Virchow.[2] One of these, a young white stallion, with melanosis of the anus, transmitted this disease to all its white descendants, whereas those of a darker colour escaped. From horses thus bred, the disease became widely diffused throughout the neighbouring country.

This is the only instance of the kind I have met with in the animal world; but, when attention is specially directed to this subject, no doubt others will be forthcoming.

### Heredity of Non-malignant Tumours.

Here it may be mentioned, that similar examples of multiple heredity occur also, in those subject to various non-malignant tumours.

Thus, Beyca[3] met with uterine myomata in four sisters, whose mother, aunt and grandmother had all been affected in the same way; and, a family of nine sisters, furnished Lawrie[4] with five instances of uterine myomatous disease, and five of cataract—three of the myomatous sisters having also the latter affection. Doran and Engeström have also each found uterine myomata in three sisters.

[1] Siebold has seen twins with six digits on each hand and foot; and Delbarre twins, each with a supernumerary right thumb.

[2] "Path. des Tumeurs," t. ii., p. 236.

[3] *American Journal of Obstetrics*, etc., vol. xliii., p. 703.

[4] *British Medical Journal*, 1904, vol. i., p. 357.

An instance of ovarian cystoma in five sisters, has been reported by Keith;[1] similar disease in a mother and her two daughters, by Simpson;[2] while Löhlein[3] met with bilateral ovarian cystoma, in three sisters; and Hue[4] with bilateral ovarian dermoids, in two sisters.

Broca[5] knew a lady and her three daughters, who had fibro-adenoma of the breast.

Multiple adenoid polypi of the rectum were found by T. Smith, in three members of a family of six; and in Child's previously cited case of cancer of the rectum in three sisters, two were affected also with multiple polypi of the part.

Multiple exostoses often manifest the same peculiarity in a marked degree: thus, in an instance recorded by Reclus, a man and his three sons were all affected in this way, as also was his sister, her daughter, four children of the latter, and seven grandchildren. In a similar case recorded by Teissin, three children of one family were thus affected, as well as their father and paternal grandfather. Here there was inheritance in the direct line, in three successive generations.

An interesting example of hereditary multiple angiomata of the skin and mucous membranes, in a mother, her three sons and one daughter, has lately been recorded by F. P. Weber, who cites similar cases by Osler and Kelly.

In like manner, Nicolle and Halipré have met with thirty-six cases in six generations, of a peculiar dystrophy of the hair and nails.

These examples suffice to make clear the similarity between malignant and non-malignant tumours, in respect to this form of heredity.

### Homotopic Transmission.

A remarkable feature about many cases of inherited cancer and other tumours is that the disease, like normal structure, is homotopic in its transmission; that is, it attacks the corresponding organ in each of the related individuals. This is especially noticeable in Sibley's case, where the mother and her five daughters all had cancer of the *left* breast; in Guthmann's case of cancer of the *corpus* uteri in three sisters; in Silcock's case of melanotic sarcoma of the choroid of the *left* eye in three generations; in the Bonaparte family, where the stomach was the part affected in every instance; in Warren's case of cancer of the penis in four generations etc.

Although this form of transmission often defaults, it is nevertheless noteworthy that, on the average—taking all the seats of inherited cancer into consideration—homotopic transmission preponderates.

Thus, of the 48 seats of inherited cancer, in my analysis of the family history of 136 cases of mammary cancer in women, the breast was the organ affected in 19; similarly of the 15 seats of the disease inherited from Madame Z., who had mammary cancer, in 9 the breast was affected; and of the 32 seats of hereditary disease, noted in my analysis of the family history of 142 uterine-cancer cases, in 13 the uterus was the part affected.

1 *British Medical Journal*, 1878, vol. ii., p. 593.
2 *Lancet*, 1905, vol. i., p. 799. 3 *Monatschr. f. Geb. u. Gyn.*, February, 1896.
4 *La Rev. Méd. de Normandie*, July 25, 1904. 5 "Traité des Tumeurs," t. i., p. 156.

The tendency to homotopic transmission may thus be taken as the established rule, although the number of cases in which heterotopic transmission occurs is by no means inconsiderable. I can discover no ground for the dictum, that homotopic transmission is especially apt to prevail among near relatives, and heterotopic transmission among distant ones.

From the foregoing facts, it may be inferred that the molecular protoplasmic disturbance, which eventuates in inherited malignant disease, affects the whole of the epithelial or connective-tissue elements of the body, as the case may be; but that its influence is most potent in that part, which corresponds to the dominant seat of the disease in affected relatives. Such indications point to intrinsic rather than to extrinsic, causative conditions.

### Family History Analyses.

In further illustration of this subject, I append analyses of the family history of a series of mammary and uterine cancer patients, so as to show the relations affected and the seats of the disease.

The family histories of 136 women with *mammary* cancer, yielded on analysis the following particulars:

| | |
|---|---|
| Father's father (in two families) .. .. .. .. | Nose.<br>Œsophagus. |
| Father's mother (in two families) .. .. .. .. | Breast.<br>Breast. |
| First cousin of father's mother (in one family) .. .. | Œsophagus. |
| Father (in five families) .. .. .. .. .. | Breast.<br>Lip.<br>Hand.<br>Internal.<br>Liver. |
| Father's sister (in ten families) .. .. .. .. | Breast (5).<br>Mouth.<br>Face.<br>Scalp.<br>Liver.<br>Internal. |
| Father's mother (in three families) .. .. .. .. | Breast.<br>Uterus.<br>Locality not stated. |
| Sister of mother's father (in one family) .. .. .. | Breast. |
| Mother (in seven families) .. .. .. .. .. | Uterus (2).<br>Stomach.<br>Breast.<br>Tongue.<br>Internal (2). |
| Mother's sister (in six families) .. .. .. .. | Breast (4).<br>Internal.<br>Tongue. |
| Mother's brother (in one family) .. .. .. .. | Groin. |
| Female cousin on mother's side (in two families) .. .. | Breast.<br>Locality not stated. |
| Patient's sister (in five families) .. .. .. .. | Breast (3).<br>Uterus.<br>Locality not stated. |
| Patient's brother (in two families) .. .. .. .. | Throat.<br>Back. |
| Patient's daughter (one family) .. .. .. .. | Internal. |

In eight of these families the disease had involved more than a single member: in one family seven members were affected, in another four, and in six families three members were attacked. The disease prevailed in the families of both parents, in four instances.

The above 48 seats of hereditary disease may be grouped thus: breast 19, internal 6, uterus 4, liver 2, œsophagus 2, all others 15.

The records of the family history of 142 consecutive *uterine* cancer patients, yielded the following results:

| | |
|---|---|
| Father's brother (in one family) .. .. .. .. | Face. |
| Father's brother and three cousins (in one family) .. | Stomach (brother).<br>Breast (female cousin).<br>Neck (male cousin).<br>Foot (male cousin). |
| Father's sister (in three families) .. .. .. .. | Uterus.<br>Intestine.<br>Arm. |
| Maternal grandmother (in one family) .. .. .. | Uterus. |
| Mother (in nine families) .. .. .. .. .. | Uterus (2).<br>Breast (2).<br>Stomach (2).<br>Intestine.<br>Abdomen.<br>Face. |
| Mother's sister (in six families) .. .. .. .. | Uterus (2).<br>Breast (2).<br>Locality not stated (2). |
| Mother's brother, and child of mother's sister (in four families) .. .. .. .. .. .. .. | Stomach (brother).<br>Face (brother).<br>Locality not stated (brother).<br>Stomach (sister's child). |
| Patient's sister (in eight families) .. .. .. .. | Uterus (6).<br>Breast (2). |
| Patient's brother (in one family) .. .. .. .. | Stomach. |
| Patient's daughter (in one family) .. .. .. .. | Uterus. |

These 38 seats of hereditary disease may be grouped thus: uterus 13, breast 7, stomach 6, face 3, locality not stated 3, intestine 2, abdomen, arm and foot, each 1.

In two of these families more than a single relative was affected: in one of them all the affected relatives were on the mother's side, and in the other all were on the father's side.

### General Conclusions as to Cancer Inheritance.

In order to ascertain the frequency of cancer inheritance, I have made an analysis of the records of the family history of numerous cancer patients with the following results:

Of 142 cases of uterine cancer, there was history of heredity in 28 (19·7 per cent.).

Of 136 cases of mammary cancer, there was history of heredity in 33 (24·2 per cent.).

Of 92 other female cancer cases, there was history of heredity in 22 (23·9 per cent.).

Thus, of these 370 female cancer patients, there was history of heredity in 83 (22·4 per cent.).

Of 209 men suffering from cancer, there was history of cancer heredity in only 23 (11 per cent.). I attribute this difference to the fact, that the men knew so much less than the women, of the details of their family history.

From whatever point of view the subject is regarded, these foregoing are very high percentages. Many anomalies well known to be hereditary, yield on inquiry a much lower proportion; for instance, of 92 cases of supernumerary mammary structures analysed by Leichtenstern, there was history of heredity in only 7, or in 7·6 per cent. In my opinion, data such as the above, are of themselves presumptive evidence of the hereditability of cancer; for, it is certain, that no such great proportion of cancerous relatives is to be found, among the relatives of the non-cancerous.

Thus, of 101 women with non-malignant tumours, there was history of cancer in only 16 families (15·8 per cent.). The above data were collected by myself, and the inquiries were made with equal care in both sets of cases.

The proportion of women with cancer of the breast, among whose relatives there was a history of cancer, has been estimated by Butlin at about 37 per cent., by Nunn at 29·3 per cent., by myself at 24·2 per cent., and by Leaf at 23 per cent.; whenever inquiries of this kind are made, in a careful and systematic manner, the proportion of relatives affected will always be found to vary within these limits or in close approximation thereto.

When therefore an inquiry was lately made at the Middlesex Hospital,[1] as to the influence of heredity in cancer, it is surprising to find that the basis on which Karl Pearson was invited to exercise his well-known biometrical skill was; that the proportion of cancerous relatives amounted only to 8·56 per cent., of 1,000 female cancer patients interrogated.

With regard to this result, I am able to state positively of my own knowledge, that inquiries yielding such a low percentage of heredity, must necessarily have been carried out in a careless and perfunctory manner; and, consequently, conclusions resting on such a basis are destitute of any scientific validity. When, therefore, it is claimed that this inquiry has proved that cancer is not a hereditable disease, it will be well to recollect the worthless nature of the substratum, on which this conclusion is based. This Middlesex hospital fiasco ought to become memorable, as a warning example of the pitfalls likely to overtake those who indulge in biometrical flights, without having made adequate antecedent survey of the actual field of operations. In a matter of this sort we must remember that error does not become truth, because it is repeated thousands of times by thousands of persons.

From the foregoing facts it may be gathered, that the transmission of

[1] *Archives of the Middlesex Hospital*, 1904, vol. ii., pp. 104 and 127; also *ibid.*, vol. v., p. 103.

malignant and other tumours by inheritance, takes place in accordance with the same general laws that govern physiological heredity; but, whereas, under physiological conditions, "the inheritance of any character whatever is the rule, and non-inheritance the anomaly," under pathological conditions—which imply failure or undoing of evolution—the tendency is just the converse: hence, with favourable circumstances, morbid states of this kind tend to die out in the course of transmission (*vis medicatrix naturæ*). In this consideration, there is assurance of the feasibility of prevention.

In accordance with these indications, I find that the tendency to cancer may be transmitted directly or through parents; indirectly or through collaterals; and by reversion (atavism), after skipping one or more generations. Examples of single-family prevalence, such as I have cited in the early part of this chapter, may probably be included under the last heading.

In the foregoing analyses, there was history of the transmission of cancer directly from parents, in about 8 per cent. of the total cases.

It rarely happens that both parents are cancerous; but, such an unfortunate combination, undoubtedly increases the proclivity to morbid inheritance.

Thus, of 136 family histories of breast-cancer patients investigated by me, in only 2 instances were *both* parents cancerous. These marriages produced 7 children, of whom 2 had died of cancer, or 1 in 3·5. Seven marriages, in which only *one* parent was cancerous, produced 62 children, of whom 10, or 1 in 6·2 had become cancerous. Six marriages, in which although neither parent was cancerous, the disease existed in their *collaterals*, produced 41 children, of whom 8, or 1 in 5·1 had become cancerous.

In spite of the numerical inadequacy of these data, I think this analysis gives fairly correct indications.

The phenomena of inheritance teach us, that the actual product of a fertilized germ never represents the full measure of its potentiality. Only a portion of the many varying tendencies inherited by the reproductive cells, from their long line of ancestors, are actually evolved in each generation. Hence, in normal heredity, we constantly see transmitted, besides developed structures, certain tendencies and predispositions.

Thus, the male and female secondary sexual characters are transmitted through each sex, though usually developed in one alone. Similarly, tendencies are transmitted through the earlier years of life, that are only subsequently developed. In like manner, we often see qualities transmitted in a latent state through one or more generations, and then suddenly developed, as in the wonderful phenomena included under the term "reversion." By virtue of these considerations, it has been truly said, that to know a man well, we must know his relations—grandparents, parents, uncles, aunts, cousins, brothers, sisters, children—in them we shall often see developed his own latent tendencies. For this reason, those who neglect collaterals in studying heredity, are greatly in error.

It not infrequently happens that such latent tendency to disease in ancestors, although it never becomes effective in them, nevertheless does so in their descendants. Thus, cases occur in which cancerous grandparents transmit the disease to their grandchildren, while their own offspring escape (atavism), as of our own royal family.

This happened in seven of the 136 cases of cancer of the female breast analysed by me, or in 5·1 per cent. In three of these cases, the disease was inherited from the maternal grandmother, in two from the paternal grandmother, and in two from the paternal grandfather. In three cases, the locality affected in the grandparents, as in the grandchildren, was the breast; in the other four cases, the localization of the disease in the grandparents, differed from that in the grandchildren. Whether cancer is ever transmitted by reversion, after skipping more than a single generation—as often happens in physiological heredity—I am unable to state, and I know of no facts bearing directly on this point; but, on *a priori* grounds, it seems probable; and this may be the explanation of such remarkable examples of single-family prevalence, as I have instanced in the early part of this chapter.

Much commoner than true atavism, or than heredity by direct descent from parents, is a form of inheritance in which the disease is transmitted through parents etc., who themselves never manifest it, although their sisters, brothers or other relatives do. On reference to my analysis of mammary-cancer cases, it will be seen that the inherited disease manifested itself, in this way, in the father's sisters in ten families, the breast being the organ affected in five; and in six families in the mother's sisters, the breast being affected in four.

It will generally be found that the birth of the subjects of direct cancer heredity, dates from a period long anterior to that at which the disease appeared in their parents. Thus, in Broca's case, the four daughters of Madame Z., who all died cancerous, were born fifteen, twenty-five, twenty-six and thirty years respectively, before the period when their mother died of the disease—that which was then latent in the parent was transmitted potentially to the offspring.

It is a legitimate inference from what has been stated, that the special tendency to cancer is of gradual evolution; and that, without this antecedent preparation, the disease can seldom be developed under ordinary circumstances.

Inherited cancer manifests itself much more frequently in the female, than in the male relatives, although the disease is as often derived from the father's as from the mother's side of the family. My analyses show this very well. Thus, of 47 affected relatives in the mammary-cancer series, there were 10 males to 37 females; and of 38 relatives in the uterine-cancer series, 8 were males and 30 females.

In cases of multiple family cancer, this tendency of the inherited disease to repeat itself unduly in the female sex is especially noticeable. Thus, in Broca's case, all the persons attacked but one, were females. Of the 19 daughters and granddaughters of Madame Z., who attained the age of thirty, 14 became cancerous; but of 7 males only 1 was thus affected.

As in normal heredity—but with less constancy—cancer tends to appear in the offspring, at about the same age that it appeared in the ancestor. Hence, like gout, cataract, insanity, and some other heritable conditions, the disease usually does not manifest itself until an advanced period of post-natal life.

It has been suggested that: "The nearer to the cancer age, in a parent, a child is begotten, the greater is the probability that a tissue proclivity to cancer will be inherited." I have been unable to find any evidence in support of this dictum; but I know of several circumstances that seem to negative it. As I have previously indicated, the subjects of uterine and mammary cancer whose life-history I have studied, married earlier and had more children than the generality of women; and, if we study the national statistics relating to the proportion of minors married and the age at marriage, during the last half-century, it will be found—although there have been very marked fluctuations in these respects—that no corresponding alterations have ensued in the incidence of the constantly increasing cancer mortality.[1]

It has also been suggested, that during the course of its transmission by inheritance, the tendency of malignant disease may be transmuted into some form of non-malignant tumour disease. On *a priori* grounds, I have no objection to offer to this suggestion; but the facts collected by me show, that the existence of such a coincidence in the family history of cancer patients, is most exceptional. Thus, the family history of 345 female cancer patients, gave evidence of non-malignant tumours only in 13 instances, or 3·7 per cent.

With regard to the influence of consanguinity, inquiries were made of thirty-three women with mammary cancer, two of whose parents were blood relations.

In one of these families, the parents being first cousins, the father died of heart disease, aged sixty-six, his father having died insane; the mother died, aged seventy-eight, of dropsy: there were five children of the marriage, of whom two died in infancy, and two sisters were alive and well; there was no history of cancer, tumour or phthisis in this family.

In the other case, the parents were third or fourth cousins, the father died, aged fifty-five, of phthisis, his mother having died of cancer of the breast; the mother died aged eighty, of old age.

Similar inquiries were made of fifty-five uterine-cancer patients, but in only one instance were the parents blood relations.

In this family, they were first cousins, and both parents were still alive and well—the father aged seventy-five, the mother aged seventy; their offspring comprised ten children, and there was no history of cancer, phthisis, or insanity in the family.

### Hereditary Proclivities Correlated with Cancer.

Study of the family history of a large number of cancer patients shows, that certain hereditary proclivities predominate among the relatives, as follows:—

[1] *Vide* Chapter XVI.

1. In the preceding chapter, I had occasion to set forth the various inter-relations of cancer and tubercle, as indicated by the life-history of cancer patients; it now remains for me to point out the inter-relations of these maladies, as revealed by study of the family history.

In this connexion, the first fact to attract attention is, that pulmonary *tubercle* is by far the most prevalent disease among the relatives of cancerous persons. Such a result is only what might have been expected *a priori*, considering the frequency of tuberculous disease in the community at large; but, a great mistake has been made in taking it for granted, on this account, that the relatives of cancerous persons have no special proclivity to tubercle. On the contrary, as I shall proceed to show, such persons are very much more prone to it than the rest of the community; indeed, their liability to phthisis is so considerable, as even to equal that of the phthisical themselves.

No statistics show a greater amount of heredity in phthisis than Dr. R. Thompson's,[1] because he has included in his list only those cases in which the family history had been very completely recorded. He obtained history of heredity in 44 per cent. of 5,000 consecutive phthisical cases—58 per cent. in females, and 36 per cent. in males. Now, my analysis of the family history of 134 women with mammary cancer, shows a history of phthisis in 55 per cent., which is almost as high a proportion as Thompson's; similarly, of 129 uterine-cancer patients, there was family history of phthisis in 60, or in 46·5 per cent.

The amount of hereditary phthisis among the rest of the community, is certainly very much less than this; it has been estimated by Dovey,[2] from analysis of the family history of 409 non-consumptive life-policy holders, at 10·8 per cent. Kuthy's[3] analysis of the family history of 108 non-tuberculous persons, gives a history of tubercle in 28·5 per cent., which is the highest estimate I know of. Nothing, therefore, can be plainer, than that the relatives of cancerous patients are very much more prone to tubercle, than the rest of the community. This is borne out, by the results deducible from my analysis of the causes of death of the brothers and sisters of patients with mammary cancer, in 88 families. These families averaged 8·8 members each, in all 774 individuals. Now, one or more deaths from phthisis took place in 40 of these families. Supposing only a single death to have occurred in each of them, this would be equivalent to 1 death from phthisis in 19 members; whereas, the mortality from phthisis in the general population in 1885, amounted only to 1 in 570. Similarly, among 83 fathers of mammary-cancer patients, who had died of various causes, the mortality from phthisis was 22, or 1 in 38; among 71 mothers it was 18, or 1 in 39; thus, among these 154 parents, it was 40, or 1 in 3·8; whereas, the ratio of deaths from phthisis to the total mortality in the general community, in 1885, amounted only to 1 in 11. Analyses of the family history of other forms of cancer, yield similar results.

Long study of the family history of cancer patients has convinced me, that most of the latter are the *surviving members of tuberculous*

[1] "Family Phthisis," London, 1885.
[2] Cited by Thompson (*op. cit.*, p. 16).
[3] *Pest. Med. Chir. Presse*, 1894, No. 51.

*families;* and the facts just cited confirm this belief. Hence, I conclude that no hereditable condition is more favourable to the development of cancer, than that which gives proclivity to tubercle.

Another consideration which accords with the foregoing is, that in families where cancer prevails—according to Moore—the elder members are more prone to become cancerous than the younger ones, the first-born being the most liable; whereas, with regard to phthisis, it has been shown by Thompson, that the younger members are the more liable—the greatest liability being with the last born.

According to Virchow,[1] predisposition to tubercle is always concomitant with special proclivity to inflammations. Ricochon[2] has shown, that congenital malformations occur with undue frequency in tuberculous families; and Critzmann found that a tendency to malformations and cancer occurred alternately in certain families.

2. If similar investigations were set on foot with regard to other diseases, I believe it would be found that the tuberculous predisposition gives proclivity to many of them, as, for instance, it certainly does to *insanity*. Thus, Clouston[3] found tuberculous deposits twice as often in the bodies of those who died insane, as in the bodies of those who died sane; and he has proved, that hereditary predisposition to insanity is much greater among the tuberculous, than among the non-tuberculous. In this connexion it is worthy of note, that the relatives of cancerous persons are more prone to insanity, than are the relatives of the non-cancerous; at least, this is the conclusion I draw from the fact, that 51 female cancer patients under my observation gave a family history of insanity in 7 cases, or in 13·7 per cent.; whereas, 29 women with non-malignant neoplasms, knew of insane relatives only in 3 instances, or in 10·4 per cent.; and the latter is probably a higher percentage than would be met with in the general community.

In his special Report on cancer in Ireland, the Registrar-General remarks:[4] "In a large number of instances where members of a family are afflicted with cancer, other members suffer from lunacy, idiocy etc. [illegible]

Ricochon[5] also found indications of a certain relationship between tubercle, neuropathies and cancer: thus, 53 individuals affected with phthisis, had 181 tuberculous, 83 neuropathic, and 28 cancerous relatives.

In the preceding chapter, I showed that the liability of insane persons to become cancerous, is decidedly below the average.

From the foregoing considerations, it appears as if predisposition to insanity, like predisposition to tubercle—with which indeed it is often allied—gives proclivity to cancer, although developed insanity—like active tuberculous disease—seldom coexists with cancerous lesions.

3. Many authors regard *apoplexy* as a manifestation of the same disposition, of which insanity is also an outcome; and my analysis shows that this disease is unduly prevalent among the relatives of

1 "Pathologie des Tumeurs," 1871, t. iii., p. 164.
2 *Rev. de la Tuberculose*, t. i., p. 11.
3 Cited by Maudsley, "Pathology of Mind," p. 112.
4 Supplement to Thirty-second Annual Report of the Registrar-General of Ireland.
5 *Op. cit.*

cancerous persons. Thus, of 154 parents of women with mammary cancer, who died of various causes, 17 died of apoplexy, or 1 in 9; whereas, the ratio of deaths from apoplexy to the total mortality of the general population in 1884, was only 1 in 36. Similar undue frequency of this disease, is noticeable among the brothers and sisters of these cancer patients; for, while 1 in 258 of the latter died of apoplexy, the mortality from it in the general community amounted, in 1884, only to 1 in 1,841.

4. As mentioned in the preceding chapter, the members of cancer families have an undue proclivity to *arthritic manifestations.*

5. There still remain to be considered two other proclivities, to which the members of cancer families are remarkably subject, viz., longevity and great reproductive fecundity.

The evidence furnished by my analyses as to the *longevity* of the parents of cancer patients, is of the most striking and conclusive kind. To prove this it will suffice to mention only a few of the leading facts, derived from the mammary-cancer analysis.

Of 112 dead fathers 14 attained the age of eighty, which is equivalent to 1,250 per 10,000; whereas, in the general population, only 463 males live to this age out of 10,000.

Of 103 dead mothers 17 attained the age of eighty, which is equivalent to 1,650 per 10,000; whereas, in the general population, only 682 females live to this age out of 10,000.

Of these 215 dead parents 2 attained the age of ninety-five, which is equivalent to 93 per 10,000; whereas, in the general population, only 21 per 10,000 live to this age.

At first sight this result appears to be in contradiction with the conclusion previously arrived at, that the relatives of cancer patients are specially liable to pulmonary tubercle; but, it must be borne in mind, that these cancer families are generally exceedingly numerous. Striking confirmatory evidence is furnished, by inquiring into the family history of centenarians and aged persons; whence it appears, that a large proportion of these—20 per cent. in the case of females—are the surviving members of phthisical families. It is evident, therefore, that the constitutional peculiarity which is associated with tubercle, is by no means incompatible with longevity.

6. Equally conclusive is the evidence as to the great *fecundity* of cancer families.

Thus, 110 of these mammary-cancer families, averaged 8·8 members in each family, or 968 members in all; whereas, according to Farr, in the general community the average number to a family at about this period was 4·6, so that an equal number of families would include only 506 members.

Inasmuch as a tendency of twinning usually goes with excessive fertility, it is probable that an undue proportion of twins occurs in these cancer families, as Critzmann has indicated; and this is quite in accord with other facts ascertained by me, as to the sexual life of female cancer patients, to which I have previously referred, viz., early puberty early marriage, great fertility, late climacteric etc.

In support of his thesis, Critzmann[1] has related the following remarkable history, in which those of the family who were not twins, died of cancer :—

The mother died of cancer of the breast, after having given birth to twins (A) ; and one daughter (B), who died of phthisis.

Both of the twins died of non-cancerous disease.

One of these twins had a daughter (A′), who died of cancer of the breast ; and her child (A″), died of cancer of the stomach.

This last child (A″) gave birth to a daughter (E), who died of cancer of the stomach ; and to two twins (C) and (D), both of whom were free from cancer, and lived to a considerable age.

The twin (C) had three children, of whom one daughter died of cancer of the stomach and ovary, and another daughter of cancer of the stomach. The latter gave birth to a son, who died of cancer of the testis ; and to a daughter, who was alive and well, when seen by the author, being the mother of two pairs of twins, all of whom were alive and well.

The twin (D) died childless.

I have often had occasion in the course of this work, to refer incidentally to the analogies between local anomalies *per excessum*, and tumours—malignant and non-malignant—pointing out that no sharp line of distinction can be drawn between them, without arbitrarily severing the chain. In this connexion, it is interesting to find that a similar kind of alternation of twins with local anomaly *per excessum*, has been noted by F. Galton ;[2] thus, referring to a family remarkable for its twins, he says : " Whenever single children were born, they always had six fingers and six toes ; but, the sets of twins, never had." In both these families we evidently have to do with constitutional tendency to over-development, manifesting itself in various forms, *e.g.*, in twins, in anomaly *per excessum*, and in cancer.

The foregoing conclusions as to the influence of heredity in cancer, although based mainly upon facts derived from the study of the family history of women with cancer of the breast and uterus, are, nevertheless, as I have specially ascertained, equally valid for cancer of all parts of the body.

In the present transitional state of fundamental conceptions relating to physiological heredity, it seems best to abstain from interpreting the facts adduced in this chapter in terms of the Mendelian theory ; although I believe the time will soon come, when it will be advantageous to review the subject from this standpoint. Even now it seems clear that the great prophylactic question is : How, in breeding, to render a dominant tendency to cancer, recessive ?

At any rate, it is perfectly evident from what has been stated in the course of this chapter, that those pathologists whose horizon does not extend beyond cells and microbes, have overlooked the chief factor in the cancer problem—that is to say, predisposition.

[1] *Bull. Méd.*, November 7, 1894.
[2] *Journal of the Anthropological Institute*, 1876, vol. v., p. 327.

## CHAPTER XVIII

# THE INITIAL SEATS OF TUMOURS, AND THEIR RELATIVE FREQUENCY

JUST as, under physiological conditions, every organ and part of the body has its proper life or autonomy; so, under pathological conditions, each organ and part likewise manifests an individuality of its own, the effect of which is very noticeable in the structure and qualities of every kind of tumour arising from it.

The much greater frequency with which tumours arise in some organs and parts of the body than in others, is an illustration of this; and, even within the limits of particular localities, areas unduly prone to tumour formation can always be discriminated.

Hence, no study of the life-history of tumour processes can be complete, which ignores pre-existing structural peculiarities.

Perhaps the most generalized statement that can be made about these tumour areas is: that they are parts of the body unusually rich in cellular elements, still capable of growth and development.

In a previous chapter,[1] I have pointed out that the localities specially prone to originate malignant tumours in infancy and early life, are very different from those whence such tumours are apt to arise at later periods; and, for further particulars relating to these, reference may be made to that writing.

The following investigation as to the initial seats of tumours and their relative frequency, in adult life, is based upon data derived from the annual reports of the registrars of four large London hospitals (Middlesex, University College, St. Bartholomew's and St. Thomas'), during a period of from sixteen to twenty-one years.

The analysis comprises 15,481 consecutive examples of primary tumours of all parts of the body, in persons of both sexes; and it shows that their site incidence and distribution were as follows:—

[1] Chapter XV.

## TABLE I.

SHOWING THE RELATIVE FREQUENCY OF THE DIFFERENT VARIETIES OF TUMOURS.

| Kind of Tumour. | Total Number of Cases. | Males. | Females. | Males. Per Cent. | Females. Per Cent. |
|---|---|---|---|---|---|
| Epithelioma (*vel* Carcinoma) .. .. | 7878 | 2861 | 5017 | 36 | 64 |
| Sarcoma [1] .. .. .. | 1350 | 702 | 648 | 52 | 48 |
| Fibroma .. .. .. | 1661 | 176 | 1485 | 10 | 90 |
| Lipoma .. .. .. | 561 | 173 | 388 | 31 | 69 |
| Adenoma .. .. .. | 505 | 58 | 447 | 11 | 89 |
| Papilloma .. .. .. | 386 | 137 | 249 | 35 | 65 |
| Osteoma .. .. .. | 261 | 117 | 144 | 45 | 55 |
| Chondroma .. .. | 81 | 41 | 40 | 51 | 49 |
| Angioma .. .. .. | 157 | 65 | 92 | 41 | 59 |
| Cystoma [2] .. .. .. | 1640 | 449 | 1191 | 27 | 73 |
| Unclassified [3] .. .. | 1001 | 412 | 589 | 41 | 59 |
| Total .. .. | 15,481 | 5191 | 10,290 | 33 | 67 |

From this table I have deduced the following percentages, showing the proneness of the different tissue systems to originate tumours.

## TABLE II.

SHOWING THE RELATIVE PROCLIVITY OF THE TISSUE SYSTEMS TO TUMOUR FORMATION.

| | | Per Cent. |
|---|---|---|
| Epithelial tumours (72 per cent.) | Epithelioma (*vel* carcinoma) .. .. | 54·5 |
| | Adenoma .. .. .. .. | 3·5 |
| | Papilloma .. .. .. .. | 2·6 |
| | Cystoma .. .. .. .. | 11·4 |
| Connective-tissue tumours (28 per cent.) | Sarcoma (including myxoma) .. .. | 9·4 |
| | Fibroma (including myofibroma) .. | 11·5 |
| | Lipoma .. .. .. .. .. | 3·8 |
| | Osteoma .. .. .. .. | 1·8 |
| | Chondroma .. .. .. .. | 0·5 |
| | Angioma .. .. .. .. .. | 1·0 |

A notable fact brought out by this analysis is, that of the two great tissue systems, the epithelial originates tumours much more frequently than the connective—the proportion being 72 per cent. of the former to 28 per cent. of the latter.

A further examination of the figures shows that this great preponder-

[1] Including 50 cases of myxoma (males 25, females 25); and 24 of keloid (males 11, females 13).

[2] Non-congenital cysts, 1,505 (male 392, females 1,113—ovarian 635); congenital cysts, 135 (males 57, females 78).

[3] Cerebral, 248 (males 135, females 113); cerebellar 39 (males 22, females 17); spinal cord, 6 (males 3, females 3); mediastinal, 107 (males 73, females 34); cutaneous moles, 36 (males 12, females 24).

ance of epithelial tumours, is entirely due to the large excess of malignant forms (epithelioma)—the ratio being 54·5 per cent. of the latter, to 9·4 per cent. of malignant connective-tissue tumours (sarcoma).

On the other hand, of non-malignant tumours only 17·5 per cent. are derived from the epithelial, as compared with 18·5 per cent. from the connective tissue.

Or, it may be stated in this way: 54·5 per cent. of all tumours are *epitheliomas* (*vel* carcinomas); 9·4 per cent. *sarcomas;* 24·7 per cent. *non-malignant tumours;* and 11·4 per cent. *cysts*.

Now, of all the tissues of the body, the epithelial ones have on the whole departed less from the primordial type than any others, hence their cells still retain their primitive powers of growth and multiplication in a higher degree than others (*elementi labili*): it is to this that I attribute their great proneness to originate tumours under pathological conditions.

In this connexion, some observations of Ribbert's are of importance. He has shown that cancer is most prone to arise from epithelia, in which active mitotic changes are normally always present, or in which such changes manifest themselves under certain physiological conditions (as in the mammæ and uterus); whereas, in organs whose epithelia seldom exhibit mitoses, such as the salivary glands, lachrymal glands, thyroid, thymus, male mammæ etc., cancers seldom arise. These observations give direct anatomical support to the doctrine I have long advocated on other grounds—viz., that cancers and other tumours are most prone to arise in localities where cells still capable of growth and development most abound.

With regard to the localities most prone to tumour formation, my analysis of hospital cases yields the following results:—

## TABLE III.

*A.*—SHOWING THE RELATIVE FREQUENCY OF TUMOURS AND THEIR CHIEF SEATS IN PERSONS OF BOTH SEXES.

| | Per Cent. |
|---|---|
| Uterus | 19·2 |
| Mamma | 17·5 |
| Skin | 9·4 |
| Connective tissue (general) | 7·7 |
| Tongue and mouth | 6·3 |
| Ovary | 5·8 |
| External genitalia | 5·1 |
| Bones (*ex* maxilla) | 4·0 |
| Rectum | 3·3 |
| Maxilla | 2·9 |
| Stomach | 2·6 |
| Lower lip | 2·6 |
| All other localities | 13·6 |
| | 100·0 |

Of these tumours, 19·6 per cent. arose from some part of the alimentary tract—the greatest number from the tongue and mouth.

TABLE III. (*continued*).

*B*.—SHOWING THE RELATIVE FREQUENCY OF TUMOURS AND THEIR CHIEF SEATS IN MALES.

| | Per Cent. |
|---|---|
| Skin | 16·4 |
| Tongue and mouth | 15·9 |
| Connective tissue (general) | 9·4 |
| Lip (lower) | 7·3 |
| External genitalia | 6·1 |
| Bones (*ex* maxilla) | 6·1 |
| Rectum | 5·0 |
| Stomach | 4·8 |
| Maxilla | 3·9 |
| Brain | 3·4 |
| Œsophagus | 3·1 |
| Testis | 2·0 |
| Mamma | 0·5 |
| Prostate | 0·2 |
| All other localities | 15·9 |
| | 100·0 |

41·7 per cent. of these tumours originated in the alimentary tract—the greatest number from the tongue and mouth.

*C*.—SHOWING THE RELATIVE FREQUENCY OF TUMOURS AND THEIR CHIEF SEATS IN FEMALES.

| | Per Cent. |
|---|---|
| Uterus | 28·7 |
| Mamma | 26·0 |
| Ovary | 8·7 |
| Connective tissue (general) | 6·9 |
| Skin | 5·9 |
| External genitalia | 4·6 |
| Bones (*ex* maxilla) | 2·9 |
| Rectum | 2·5 |
| Maxilla | 2·4 |
| Tongue and mouth | 1·6 |
| Brain | 1·4 |
| Stomach | 1·4 |
| Liver | 1·2 |
| All other localities | 5·8 |
| | 100·0 |

Of these tumours, 8·7 per cent. originated from the alimentary tract—the greatest number from the rectum.

These figures show the great frequency with which, in females, the reproductive organs—uterus, mamma, ovary etc.—are attacked; in fact, nearly 70 per cent. of all tumours in women arise from these organs. The very great frequency with which the uterus and mamma are affected, is particularly striking. From the fact that both of these parts are subject to remarkable post-natal developmental changes, it may be inferred that they are unusually rich in cells still capable of growth and multiplication; and it is to this that I ascribe their greater proclivity to tumour formation.

It accords with this, that tumours rarely originate from obsolete or obsolescent structures; *e.g.*, male breast, gall-bladder, clitoris, hymen, thymus, adrenals, intervertebral disks, membrana nictitans, uterus masculinus, Meckel's diverticulum, vermiform appendix, tendons, ligaments, central canal of nervous system, chorda dorsalis, urachus, coccyx, os centrale, sesamoid bones, cartilage etc.

It is equally exceptional for tumours to arise from highly specialized structures such as the heart, large bloodvessels, voluntary muscles, nerves etc.

In all such instances as the foregoing, proliferous cells are scanty or absent; and it is to this peculiarity that their comparative immunity from tumour growth may be ascribed.

### Epithelioma (vel Carcinoma).

Throughout the body malignant tumours occur with greater relative frequency than non-malignant ones; I have found the ratio to be 64 per cent. of the former, to 36 per cent. of the latter.

Of 26,722 fatal malignant tumours (males 10,476, females 16,246) tabulated in the national mortality statistics for 1900, only 1,611 (males 790, females 821) are discriminated as sarcoma, or 6 per cent.; whereas, of my 9,228 hospital malignant tumours, 1,350 were sarcomatous, or 14·6 per cent., and 7,878 epitheliomatous, or 85·4 per cent.

Of the 13,824 tumours of all kinds—the localizations of which are defined in my table—7,297 were of the malignant epithelial type (males 2,669, females 4,628).

These were distributed as follows:—

TABLE IV.

SHOWING THE LOCALIZATION OF MALIGNANT EPITHELIAL TUMOURS IN MALES AND FEMALES, AS INDICATED BY HOSPITAL STATISTICS.

MALES (2,669 CASES).

| | Per Cent. |
|---|---|
| Tongue and mouth | 26·3 |
| Skin | 14·3 |
| Lip | 12·2 |
| Stomach | 8·3 |
| Rectum | 7·5 |
| External genitalia | 6·8 |
| Œsophagus | 5·3 |
| Liver | 4·4 |
| Intestines | 1·9 |
| Breast | 0·6 |
| Prostate | 0·3 |
| All other localities | 12·1 |
| | 100·0 |

FEMALES (4,628 CASES).

| | Per Cent. |
|---|---|
| Breast | 40·3 |
| Uterus | 34·0 |
| Rectum | 4·3 |
| Skin | 4·1 |
| External genitalia | 3·4 |
| Stomach | 2·8 |
| Liver | 2·5 |
| Tongue and mouth | 2·18 |
| Intestines | 1·06 |
| Œsophagus | 0·70 |
| Lip | 0·06 |
| All other localities | 4·60 |
| | 100·00 |

This analysis shows that a large proportion of all malignant epithelial tumours (epitheliomas), originate from some part of the alimentary tract—the percentage being 41·9, some of which are not specially discriminated in the table.

The liability of males to epithelioma of this system is particularly great, no less than 68·6 per cent. of all their malignant epithelial tumours being thus located; whereas, 15·2 per cent. is the proportion for females.

In women, mammary (40·3 per cent.) and uterine (34 per cent.) forms of the disease are predominant; but, in men, the corresponding localities are seldom affected—mamma, 0·6 per cent.; prostate, 0·3 per cent.

On the other hand, in the tongue and mouth, skin, and lower lip, the proclivity of men is much greater than that of women.

The same subject from another standpoint, is further illustrated by the following data:—

## TABLE V.

SHOWING THE LOCALIZATION OF MALIGNANT EPITHELIAL TUMOURS IN BOTH SEXES.

| | Males. | Females. | Total. |
|---|---|---|---|
| Breast .. .. .. | 16 | 1863 | 1879 |
| Uterus and prostate.. .. | 7 | 1571 | 1578 |
| Tongue and mouth .. .. | 703 | 101 | 804 |
| Skin .. .. .. .. | 381 | 190 | 571 |
| Rectum .. .. .. | 199 | 202 | 401 |
| Stomach .. .. .. | 222 | 130 | 352 |
| External genitalia .. .. | 182 | 158 | 340 |
| Lip (lower) .. .. .. | 326 | 3 | 329 |
| Liver .. .. .. .. | 115 | 113 | 228 |
| Œsophagus .. .. .. | 144 | 35 | 179 |
| Intestines .. .. .. | 49 | 49 | 98 |
| Superior maxilla .. .. | 42 | 28 | 70 |
| Bladder .. .. .. | 43 | 16 | 59 |
| Testis and ovary .. .. | 27 | 27 | 54 |
| Larynx .. .. .. | 34 | 4 | 38 |
| Anus .. .. .. .. | 17 | 10 | 27 |
| All other localities .. .. | 162 | 128 | 290 |
| Total .. .. | 2669 | 4628 | 7297 |

This shows that of 1,879 consecutive cases of mammary cancer in both sexes, only 16 were of the male breast, or 1 in 117; similarly only 7 prostatic cancers were met with to 1,571 uterine cancers, or 1 in 224.

On the other hand, of 329 consecutive lower-lip cancers only 3 were in females, or 1 in 108; similarly with regard to the tongue and mouth, of 804 consecutive cancers only 101 were in females, or 1 in 7.

The foregoing data may be relied upon as representing the localization of the disease in hospital patients, but this of course implies a certain selection. Owing to this cause, the relative frequency of the disease in such localities as the breast, tongue, mouth, skin and lip, is probably exaggerated; while the liability of the stomach, liver and intestines is no doubt understated.

To correct these shortcomings in the clinical data, I append some of the chief results deducible from the national mortality statistics,[1] which refer to malignant disease in general.

Owing to a certain laxity in death certification etc., these estimates are confessedly not perfectly reliable; but, the basis on which they rest is so broad, that—in spite of this defect—they furnish valuable indications.

## TABLE VI.

SHOWING THE LOCALIZATION OF MALIGNANT DISEASE IN MALES AND FEMALES, AS INDICATED BY MORTALITY RETURNS (ENGLAND AND WALES).

| Males (9,932 Cases). | Per Cent. | Females (15,264 Cases). | Per Cent. |
|---|---|---|---|
| Stomach | 21·4 | Uterus | 23·5 |
| Liver and gall-bladder | 13·4 | Breast | 15·8 |
| Rectum | 9·6 | Liver and gall-bladder | 13·5 |
| Tongue and mouth | 6·4 | Stomach | 13·2 |
| Intestines (*ex* rectum) | 6·1 | Rectum | 5·3 |
| Œsophagus | 6·0 | Intestines (*ex* rectum) | 5·2 |
| Skin | 4·1 | Abdomen | 2·0 |
| Bladder | 2·8 | Peritoneum | 1·8 |
| Jaws | 2·7 | Ovary | 1·6 |
| Face | 2·0 | Œsophagus | 1·5 |
| Pharynx | 2·0 | Skin | 1·0 |
| Larynx and trachea | 1·8 | Bladder | 0·9 |
| Lips | 1·6 | Jaws | 0·8 |
| Testis and penis | 1·6 | Face | 0·6 |
| Prostate | 1·0 | Tongue and mouth | 0·6 |
| Breast | 0·2 | Lips | 0·2 |
| All other localities | 17·3 | All other localities | 12·5 |
| | 100·0 | | 100·0 |

This table makes it quite plain, that cancer is a disease chiefly predominant in the *alimentary tract.*

Of 25,196 cancers—in persons of both sexes—comprised in these returns, no less than 13,627 were of the alimentary tract, or 54 per cent.

Among the males, 70·6 per cent. were affected with alimentary cancer; and among the females 43·3 per cent.

Uterine and mammary cancer together, account for 39·3 per cent. of the female cancer mortality.

It will be noticed that malignant disease of the liver, occupies a very exalted position in these—and in fact in all—mortality returns.

There is great diversity of opinion among pathologists, as to the frequency of primary malignant disease of the liver: some think that it is common, and others that it rarely occurs. The truth probably lies between these extremes. Secondary cancer of the liver is certainly of vastly more frequent occurrence, than the primary form; and it is often difficult clinically to discriminate between the two. Owing to this cause, the frequency of primary malignant disease of the liver is no doubt overstated in the national mortality statistics; but, even when allowance has been made for errors of this kind, I believe the mortality from this cause is considerable.

[1] Sixty-first Annual Report of the Registrar-General for England and Wales.

In further illustration of this subject, I give below the chief results of an analysis of the United States mortality returns, as detailed in the Twelfth United States Census Report for the year 1900.

TABLE VII.

SHOWING THE LOCALIZATION OF CANCER IN MALES AND FEMALES, AS INDICATED BY THE MORTALITY RETURNS (UNITED STATES).

| Males. | Per Cent. | Females. | Per Cent. |
|---|---|---|---|
| Stomach .. | 43·0 | Uterus .. | 27·6 |
| Liver .. | 14·5 | Stomach .. | 24·4 |
| Head, face, and neck .. | 10·4 | Breast .. | 15·7 |
| Tongue, mouth, and throat .. | 9·5 | Liver .. | 12·5 |
| Abdomen .. | 9·2 | Abdomen .. | 7·6 |
| Rectum .. | 5·4 | Rectum .. | 3·5 |
| Bladder .. | 2·5 | Head, face, and neck .. | 3·1 |
| Larynx .. | 1·0 | Tongue, mouth, and throat .. | 1·6 |
| Breast .. | 0·7 | Ovary .. | 0·9 |
| Penis .. | 0·3 | Bladder .. | 0·6 |
| Testis .. | 0·1 | Larynx .. | 0·1 |
| All other localities .. | 3·4 | All other localities .. | 2·4 |
| | 100·0 | | 100·0 |

This table shows even greater predominance of cancer of the alimentary tract, than the English one—66·7 per cent. of all cancers in both sexes being thus situated.

Of the male cancer mortality 81·6 per cent. was of the alimentary system, and of the female cancer mortality 51·8 per cent.

### The Proclivity of Certain Regions in Particular Organs etc.

Another matter deserving notice in this connexion, is the great proclivity of certain regions of particular organs to cancer and tumour formation, and the comparative immunity of other regions.

Even the different tissue constituents of the various organs, vary greatly in this respect; and that when they are genetically akin.

Thus, while countless thousands of cancers have sprung from the uterine mucosa, I know of only a very few instances in which the disease has originated from its peritoneal lining.

Again, the mucosa of the lower segment of the uterus (cervix etc.) is very much more apt to generate cancer, than that of its upper segment (corpus)—the percentage proportion being 97 per cent. in the former locality, to 3 per cent. in the latter.

Strange to relate, the proclivity of the uterine musculature to originate myoma in its upper and lower segments, is just the converse of that of its mucosa to originate cancer; for, while over 90 per cent. of all uterine myomata originate in the corpus, only about 10 per cent. spring from the cervix.

Another illustration of the same peculiarity is seen, in the great diversity in liability to cancer and other tumours, manifested by the various organs evolved from the different segments of the Müllerian ducts. Of these organs, only the uterus manifests great proclivity to tumour formation—for the vagina and Fallopian tubes are seldom affected.

Thus, of 9,227 consecutive tumours in women tabulated by me, 2,648 were of uterine origin (cancer 1,571, sarcoma 2, myoma 1,073, and cystoma 2); but only 54 arose from the vagina (cancer 40, sarcoma 2, myoma 3, and cystoma 9); while, not a single case, is credited to the Fallopian tubes!

From this it may be inferred, that the biological peculiarities which determine a given part to tumour formation, depend more upon functional than upon genetic considerations; the vagina, for instance, is physiologically more akin to the vulva than to the uterus, and the results of this similarity are apparent in its pathological neoplastic variations.

In other parts of the body similar conditions prevail.

Thus, in the *female breast*, cancerous tumours are much more prone to develop in some parts of the organ than in others.

The extreme rarity of epithelial cancer of the nipple and areola is, for instance, very remarkable; for, as we have seen,[1] less than 1 per cent. of all mammary cancers thus originate. Cancer arising from any other part of the mammary integument is so exceedingly rare, that neither Velpeau nor Billroth, with their large clinical experience, ever met with a single instance; and the number of such cases even now on record is less than a dozen.

Again, cancerous tumours of the mamma form much oftener in the peripheral, than in the central part of the gland. Of 132 cases under my observation, in 90 (68 per cent.) the tumour was peripheral; and in 42 (32 per cent.) central. This accords with what I have previously pointed out, as to the special tendency of cancers to arise in the seats of greatest post-embryonic developmental activity, where cells still capable of growth and development most abound; that is to say, in the immediate vicinity of the acini and smallest ducts, which are much more numerous in the peripheral than in the central part of the gland. Here it may be mentioned, that the great majority of mammary cancers are acinous derivatives, while only a small minority spring from the tubular structures of the gland, and hardly any from the large ducts.

With regard to the localization of the peripherally situated cancers, most of them are met with in the upper and axillary mammary segments. Thus, of 90 cases under my observation, the disease was situated in the upper segment in 46, in the axillary in 20, and in the sternal in 3. Gross' analysis of the localization of 820 cancerous tumours of the mamma, may be diagrammatically represented as follows:—

| | | | | |
|---|---|---|---|---|
| | | *Upper.* | | |
| | 206 | 90 | 55 | |
| *Axillary.* | 83 | 231 | 32 | *Sternal.* |
| | 32 | 51 | 40 | |
| | | *Lower.* | | |

A considerable number of these peripheral cancers, are situated *quite outside the mammary gland;* where, as I have elsewhere shown,[2] they originate from outlying sequestrated mammary structures, which are of common occurrence in this organ and in its vicinity.

I was able to determine that this was the condition in 13 (9·8 per

[1] Chapter XI.

[2] "Diseases of the Breast," 1894, chap. iv., p. 73: "Paramammary Tumours arising from Supernumerary Mammary Structures."

cent.) out of 132 consecutive breast cancers under my observation. Of 29 tumours that originated in this way, 15 were situated in the axilla, 8 in the sternal region, and 6 were found above the breast.

The different segments and organs of the *digestive system* manifest similar inequalities, in their proclivity to malignant epithelial tumours. Thus, as the national mortality returns show, the localization percentages of the disease in this system—in males—are as follows :—stomach 30·3, intestines 22·3, liver 19·1, tongue and mouth 9, œsophagus 6, abdomen and peritoneum 3·8, pharynx 2·9, lips 2·3, and pancreas 1·7.

If we take these segments of the alimentary canal separately, each will be found to present, within its own limits, similar diversities in proclivity to cancer.

Thus, in the *stomach*, the pylorus is attacked with much greater frequency than any other part of the organ, for Brinton and Welch's analysis of 1,524 cases—in which the seat of the disease was well defined—shows that no less than 66·3 per cent. of all gastric cancers were thus situated. Other parts of this organ are affected in the following percentage proportions :—lesser curvature 12·2, cardia 9·2, posterior surface 5·2, great curvature 2·9, anterior wall 2·7, fundus 1·2, and centre 0·3.

Inequalities of this kind are still more strikingly illustrated, in the incidence of *intestinal* cancer.

Here one is at once struck with the great predominance of the disease in the rectum—61 per cent. of all intestinal cancers being thus located, according to the mortality returns.[1] On the other hand, only 5 per cent. of all intestinal cancers arise from the great length of the small intestine—the duodenum being very rarely affected.

Of the remaining 34 per cent., one-half (17 per cent.) are located in the sigmoid flexure ; and the other half are nearly equally distributed between the other segments of the colon—with decided predominance in the descending colon. The cæcum and ileo-cæcal valve are rarely affected, and the appendix hardly ever—in fact, the percentage for all these parts taken together, hardly amounts to 0·5.

In the *rectum* itself similar phenomena are met with ; for, I have found that 54·5 per cent. of all cancers of this part, originate at from 2 to 4 inches above the anus ; while about 5 per cent. of all intestinal cancers are anal in origin.

In the *tongue*, I find that malignant tumours almost invariably arise from the epithelial elements, and hardly ever from those of the much more abundant connective tissue ; thus, of 644 primary malignant tumours of the tongue in my list, all but one (sarcoma) were of epithelial origin.

Moreover, it is noteworthy that of the epithelial elements of the tongue, it is only the epidermoidal that originate malignant tumours ; the numerous epithelial glandular structures of this organ, hardly ever being affected in this way.[2]

I have found the seats of the initial lesions of epithelioma of the tongue and mouth, in 100 consecutive cases in males, to be as follows :—

[1] Hospital data, tabulated by myself, show a still higher proportion—viz., of 466 intestinal cancers, 86 per cent. were of the rectum.

[2] For reference to a case of primary cancer of the tongue, which arose from the mucous glands of its surface, *vide* Miles, "Encyclopædia Medica," p. 290.

| | | |
|---|---|---|
| Edge of tongue[1] (middle, 21 ; base, 14 ; tip, 5 ; front, 4) .. .. | in | 48 cases. |
| Floor of mouth (near frænum) .. .. .. .. .. | ,, | 21 ,, |
| Buccal surface of cheek .. .. .. .. .. .. | ,, | 10 ,, |
| Gum .. .. .. .. .. .. .. .. .. | ,, | 5 ,, |
| Dorsum of tongue .. .. .. .. .. .. | ,, | 4 ,, |
| Empty socket of molar teeth .. .. .. .. .. | ,, | 2 ,, |
| Soft palate .. .. .. .. .. .. .. .. | ,, | 2 ,, |
| Hard palate .. .. .. .. .. .. .. .. | ,, | 2 ,, |
| Floor of mouth (other than near frænum) .. .. .. .. | ,, | 2 ,, |
| Substance of tongue .. .. .. .. .. .. .. | ,, | 2 ,, |
| Between gum and cheek .. .. .. .. .. .. | ,, | 1 case. |
| Between gum and lower lip .. .. .. .. .. .. | ,, | 1 ,, |
| Total .. .. .. | | 100 cases. |

In the *skin* similar peculiarities are noticeable ; but, in a larger proportion of cases, the disease seems to start from the glandular structures. Of 49 consecutive cases of cutaneous cancer of which I have preserved the records, 37 originated from the head, 1 from the neck, 2 from the trunk, 7 from a lower limb, and 2 from an upper limb.

Of the 37 head cases, mostly rodent ulcer, 23 originated from the nose (near the inner canthus, 10 ; the ala, 3 ; between the two foregoing, 5 ; tip of nose, 3 ; root, 1 ; middle of bridge, 1), 6 from the cheek, 3 from the lower eyelid, 2 from the forehead, 2 from the skin of the upper lip, and 1 from the external ear.

The great predisposition of the skin of the face, especially that of the nose and its vicinity, to develop cancer is very remarkable.

Of the 7 cases of cancer of the lower limb, 4 sprang from the thigh, 2 from the foot, and 1 from the knee.

Of the 2 upper-limb cancers, 1 was of the axilla and the other of the hand.

Of the 2 trunk cancers, 1 sprang from the skin of the back, and the other from that of the front of the abdomen.

It has been suggested by Cheatle,[2] that this special proclivity of certain tissues and localities to cancer is, directly or indirectly, connected with certain nerve influences—trophic—which are supposed to preside over the affected areas. This suggestion appears to me to be nothing but a hypothesis of a hypothesis, for trophic nerves and trophic areas have never been proved to exist ; and most physiologists, who have especially studied the subject, reject this theory of growth. The clinical evidence is equally unconvincing ; thus, Gowers remarks[3]: " It was once thought that there are special trophic fibres, some think so still, but evidence of their existence is difficult to discern." In the early stages of the development *ab ovo*, growth and differentiation go on in a regular and orderly manner, in the absence of nerves and bloodvessels ; and there is no valid reason for supposing that, at subsequent periods, growth is differently regulated. I am certainly unacquainted with any facts connected with the localization of cancer, that really support Cheatle's view ; and, those adduced by its author, seem to me to be altogether inconclusive.

Such facts as to the initial seats of the disease, as I have set forth in this chapter, cannot be thus explained ; and, in the case of secondary cancers, we can certainly eliminate any such hypothetical influence.

[1] Right side, 25 ; left side, 18.
[2] Transactions of the Pathological Society, London, 1903.
[3] *Lancet*, 1905, vol. ii., p. 1594.

As I have already intimated, and as I shall subsequently have occasion to show, these inequalities in morbid proclivity have nothing whatever to do with nervous or vascular influences; but they are rather the outcome of biological peculiarities inherent in the cellular elements of the affected parts, which ultimately resolve themselves into functional modifications.

## Sarcoma.

Passing now to the sarcomas of adult life, I find that most of them arise from the bones, connective tissue, and from certain organs.

My analysis of 1,350 primary sarcomas in adults, shows that of the *bones*, those most prone to be affected are the superior and inferior maxilla, the femur, humerus, tibia, innominate, scapula, and skull bones.

Next to the bones, in order of proclivity, come the female breast, genital glands, eye, parotid and skin.

Sarcomas of the soft parts of the face, neck, thigh, leg, orbit etc., are also of frequent occurrence.

The numbers for each locality, are shown in the following tables :—

### TABLE VIII.

SHOWING THE PRIMARY SEATS OF SARCOMA IN ADULTS.

GENERAL STATEMENT.

| Locality. | Total. | Males. | Females. |
|---|---|---|---|
| Bones .. .. .. .. | 385 | 217 | 168 |
| Connective tissue .. .. .. | 340 | 186 | 154 |
| Other parts .. .. .. .. | 341 | 141 | 200 |
| Unclassified .. .. .. .. | 284 | 158 | 126 |
| Totals .. .. .. | 1350 | 702 | 648 |

BONES AFFECTED.

| Locality. | Total. | Males. | Females. |
|---|---|---|---|
| Superior Maxilla .. .. .. | 102 | 53 | 49 |
| Inferior Maxilla .. .. .. | 48 | 31 | 17 |
| Femur .. .. .. .. | 61 | 34 | 27 |
| Humerus .. .. .. .. | 22 | 13 | 9 |
| Tibia .. .. .. .. | 19 | 13 | 6 |
| Innominate .. .. .. .. | 19 | 12 | 7 |
| Skull .. .. .. .. | 19 | 12 | 7 |
| Scapula .. .. .. .. | 12 | 7 | 5 |
| Fibula .. .. .. .. | 11 | 6 | 5 |
| Foot .. .. .. .. | 6 | 5 | 1 |
| Ribs .. .. .. .. | 6 | 5 | 1 |
| Sacrum .. .. .. .. | 4 | 3 | 1 |
| Ulna .. .. .. .. | 3 | 2 | 1 |
| Radius .. .. .. .. | 3 | — | 3 |
| Clavicle .. .. .. .. | 2 | 1 | 1 |
| Hand .. .. .. .. | 2 | — | 2 |
| Coccyx .. .. .. .. | 2 | — | 2 |
| Sternum .. .. .. .. | 1 | — | 1 |
| Unclassified .. .. .. .. | 43 | 20 | 23 |
| Totals .. .. .. | 385 | 217 | 168 |

TABLE VIII. (*continued*).

CONNECTIVE TISSUE.

| Locality. | Total. | Males. | Females. |
|---|---|---|---|
| Face .. .. .. .. | 20 | 12 | 8 |
| Neck .. .. .. .. | 20 | 12 | 8 |
| Thigh .. .. .. .. | 18 | 7 | 11 |
| Leg .. .. .. .. .. | 13 | 6 | 7 |
| Orbit .. .. .. .. | 12 | 8 | 4 |
| Mediastinum .. .. .. .. | 11 | 7 | 4 |
| Peritoneum .. .. .. .. | 11 | 8 | 3 |
| Multiple .. .. .. .. | 10 | 5 | 5 |
| Nose .. .. .. .. | 10 | 10 | — |
| Groin .. .. .. .. | 8 | 7 | 1 |
| Retro-peritoneal .. .. .. | 8 | 3 | 5 |
| Arm .. .. .. .. | 7 | 5 | 2 |
| Shoulder .. .. .. .. | 7 | 5 | 2 |
| Scalp .. .. .. .. | 6 | 4 | 2 |
| Abdominal wall .. .. .. | 6 | 3 | 3 |
| Forearm .. .. .. .. | 5 | 2 | 3 |
| Hand .. .. .. .. | 4 | 4 | — |
| Popliteal space .. .. .. | 4 | 2 | 2 |
| Upper lip .. .. .. .. | 4 | 2 | 2 |
| Pelvis .. .. .. .. | 3 | — | 3 |
| Peri-renal .. .. .. .. | 2 | 1 | 1 |
| Muscle .. .. .. .. | 2 | 2 | — |
| Eyelid .. .. .. .. | 2 | — | 2 |
| Foot .. .. .. .. | 1 | 1 | — |
| Infra-clavicular .. .. .. | 1 | — | 1 |
| Scapular .. .. .. .. | 1 | 1 | — |
| Back .. .. .. .. | 1 | — | 1 |
| Axilla .. .. .. .. | 1 | — | 1 |
| Gluteal .. .. .. .. | 1 | 1 | — |
| Ischio-rectal .. .. .. .. | 1 | — | 1 |
| Unclassified .. .. .. .. | 140 | 68 | 72 |
| Totals .. .. .. | 340 | 186 | 154 |

Gurlt's analysis of 741 sarcomata gives analogous results : 194 cases arose from the maxillæ (superior 96, inferior 83), 150 from the female breast, 45 from the testis, 33 from the parotid, 30 from the face, 30 from the thigh, 30 from the leg, 26 from the neck and submaxillary region, 20 from the inguinal region, 18 from the orbit, 18 from the arm, 18 from the foot, 15 from the nares, 13 from the eye, 7 from the ovary etc.

Of 162 sarcomata of the *long bones* by Gross and 36 by myself, the initial seats of the disease were, the femur in 84, tibia in 53, humerus in 29, fibula in 13, ulna in 7, radius in 8, and radius and ulna in 1 case.

Of 128 malignant *melanotic* tumours of the *skin* tabulated by Dieterich, 48 arose from the extremities, 41 from the trunk, 28 from the head, and 11 from the neck. Of Gurlt's 18 melanomata, 5 originated from the face, 3 from the leg, and 1 each from the parotid region, eye, rectum, liver, ovary, breast, abdominal wall, hand, thigh ; and 1 was of multiple origin.

Of 175 primary sarcomata of the *gastro-intestinal* tract tabulated by Corner and Fairbank,[1] the site incidence was as follows :—Œsophagus 14,

[1] Transactions of the Pathological Society, London, 1905, vol. lvi., p. 25.

TABLE VIII. (*continued*).

OTHER PARTS.

| Locality. | Total. | Males. | Females. |
|---|---|---|---|
| Breast .. .. .. .. | 95 | 3 | 92 |
| Genital glands .. .. .. | 64 | 40 | 24 |
| Eye .. .. .. .. .. | 40 | 20 | 20 |
| Parotid .. .. .. .. | 32 | 15 | 17 |
| Skin .. .. .. .. | 17 | 7 | 10 |
| Palate .. .. .. .. | 12 | 4 | 8 |
| Lymph-glands .. .. .. | 12 | 10 | 2 |
| Kidney .. .. .. .. | 8 | 3 | 5 |
| Rectum .. .. .. .. | 7 | 5 | 2 |
| Bladder .. .. .. .. | 6 | 5 | 1 |
| Tonsil .. .. .. .. | 5 | 5 | — |
| Submaxillary gland .. .. .. | 4 | 4 | — |
| Lung .. .. .. .. | 3 | 3 | — |
| Prostate .. .. .. .. | 2 | 2 | — |
| Larynx .. .. .. .. | 2 | 2 | — |
| Pharynx .. .. .. .. | 2 | — | 2 |
| Vagina .. .. .. .. | 2 | — | 2 |
| Uterus .. .. .. .. | 2 | — | 2 |
| External ear .. .. .. .. | 1 | 1 | — |
| Optic nerve .. .. .. .. | 1 | — | 1 |
| Vulva .. .. .. .. | 1 | — | 1 |
| Colon .. .. .. .. | 1 | 1 | — |
| Thyroid .. .. .. .. | 1 | — | 1 |
| Mouth .. .. .. .. | 1 | 1 | — |
| Supra-renal .. .. .. .. | 1 | 1 | — |
| Spinal meninges .. .. .. | 1 | — | 1 |
| Tongue .. .. .. .. | 1 | 1 | — |
| Brain .. .. .. .. | 1 | 1 | — |
| Unclassified .. .. .. .. | 16 | 7 | 9 |
| Totals .. .. .. | 341 | 141 | 200 |

stomach 58, small intestine 65, ileo-cæcal region 20, large intestine 11, and rectum 7.

Of the gastric sarcomata, 64 per cent. originated from some part of the organ other than the pylorus, which gave origin only to 36 per cent.

In the small intestine, the original seats of the disease were—ileum in 28 cases, jejunum in 19, and duodenum in 8.

This collection of cases comprises 3 examples of primary intestinal melanotic sarcoma—2 of the rectum, and 1 of the ileum.

Pure *myxomata*—that is to say, tumours consisting of clear, glassy, translucent substance, like that of the jelly-fish—are certainly very rare. I have met with only two or three cases of this kind. Myxomata usually comprise, besides their special structure, sarcomatous, fibrillar, chondromatous or fatty elements, which tend to obscure their glassy properties. The localities affected in my 50 cases, were as follows:—thigh 8 (males 6, females 2); parotid 4 (males 3, female 1); breast 4 (males 2, females 2); peri-renal 2 (male 1, female 1); and 1 each as follows:—popliteal (male), pectoral (female), naso-pharyngeal (male), pelvis (female), arm (female), neck (male), finger (male), loin (male), nose (female), testis, soft palate (female), and unclassified 21 (males 7, females 14).

It is interesting to note, as in the case of epithelioma, the extreme rarity of sarcoma in some situations, *e.g.*, the muscles, tendons, spleen, heart, great bloodvessels, digestive system, stomach, tongue, uterus etc.

## Non-malignant Tumours.

In the case of non-malignant tumours, similar diversities in morbid proclivity are noticeable, as may be gathered from the following items :—

*Leio-myomata* occur with extraordinary frequency in the uterus, and in the prostate ; but, in other parts of the body, they are of the greatest rarity, although leio-myomatous tissue is widely diffused.

Some pathologists deny the right of the prostatic tumours to be classed as myomata, because of the glandular structures they contain ; but, in all parts of the body where these tumours occur, it is not uncommon to find included glandular structures.

*Fibromata* usually present as polypoid outgrowths, their commonest seats being the uterus (myo-fibromatous), maxillæ (epulis), nasal fossæ, lower limb, external genitals, external auditory meatus, subcutaneous (painful tubercle), basis cranii (naso-pharyngeal), skin etc.

*Lipomata* may be either acquired, or they may already exist at birth. The latter variety is comparatively rare. Of 200 consecutive acquired lipomata, all but 5 were situated in the subcutaneous *panniculus adiposus*.

The other five were more deeply seated, either under or between the adjacent muscles. In 5 out of 190 cases, more than a single tumour was present.

The situations occupied by these tumours were as follows :—trunk 47·8 per cent.—rather more than half being situated posteriorly, chiefly in the lumbar and scapular regions : upper limb 27·8 per cent.—most of them being in the deltoid, acromial and axillary regions : lower limb 12·2 per cent.—the thigh and gluteal regions chiefly : neck 8·4 per cent. —mostly posterior : head 3·8 per cent.

*Adenomata.*—Of 505 consecutive cases, 73·6 per cent. originated in the female breast ; 12·6 per cent. in the parotid ; and 10·3 per cent. in the rectum (polypoid) ; other localities affected were the submaxillary gland, palate, sweat-glands, lachrymal gland, septum nasi and face.

*Papillomata.*—Of 386 cases, the meatus urinarius externus was the seat of the disease in 38·8 per cent. ; the skin—chiefly of the head—in 26·7 per cent. ; the external genitals (non-venereal) 15·5 per cent. ; the bladder (villous) 5·9 per cent. ; the tongue and mouth 4·9 per cent. ; the lips.2 per cent. ; the rectum (villous) 1·8 per cent. ; other seats affected were the anus, trachea and conjunctiva.

*Osteomata.*—Of 111 cases, the terminal phalanx of the great toe (subungual) was the seat of the disease in 30·6 per cent. ; the femur in

16·2 per cent. ; the tibia in 11·7 per cent. ; multiple in 9·9 per cent. ; the humerus in 9 per cent. ; the vertebræ in 4·5 per cent. ; the other parts affected being the superior maxilla, mastoid process, scapula, fifth metacarpal bone, innominate, ulna, external auditory process, metatarsal bone, terminal phalanx of middle toe (subungual—1 case). The very frequent occurrence of the subungual exostosis of the great toe, and the constancy of its attachment to the tibial side thereof, is remarkable.

*Chondromata.*—Of 72 cases, 37·5 per cent. were located in the parotid ; 22·2 per cent. in the hand ; 22·2 per cent. in the long bones ; 2·8 per cent. in the superior maxilla ; 2·8 per cent. in the submaxillary gland ; the other situations affected being inferior maxilla, female breast, testis, ischio-rectal region, lachrymal gland, toe, scapula, external ear, and mediastinum.

*Angiomata.*—Of 94 cases, 55·3 per cent. were located on the head ; 21·3 per cent. on the trunk ; 7·5 per cent. on the neck ; 5·3 per cent. on the external genitals ; 5·3 per cent. on the lower limb ; and 5·3 per cent. on the upper limb.

## Cysts.

In the distribution of cysts, the most striking features are the great proclivity to this kind of formation of the ovary, and the sebaceous glands of the skin, especially of the scalp.

Of 1,640 cysts, 91·8 per cent. were of post-natal, and 8·2 per cent. of pre-natal development.

Of the former group, 48 per cent. were ovarian or broad ligament cysts. (Of 216 cysts of this kind, 84·5 per cent. originated in the ovary, and 11·5 per cent. in the broad ligament). Sebaceous cysts (two-thirds of the scalp) amounted to 29·2 per cent. ; spermatic cord and round ligament cysts 5·2 per cent. ; female breast 4·1 per cent. ; external genitals 4 per cent. ; dental (alveolar) 1·9 per cent. ; testis 1·5 per cent. ; floor of mouth 1·4 per cent. ; and thyroid 1 per cent.

Other localities thus affected were—peri-articular, neck, parotid, thigh, kidney, omentum, cerebellum, uterus, pelvis, groin, retro-peritoneal, lip, loin, liver, humerus and finger.

Of the congenital cysts, 92·3 per cent. were dermoids : these were situated as follows :—Head, 41·6 per cent. (more than half in the orbital region) ; ovary, 35 per cent. ; neck, 17·3 per cent. ; other situations involved being the thigh, scrotum, sternum, and peritoneum.

## Summary.

In order to show the influence of locality in determining the genesis, structure, qualities and relative frequency of the different kinds of tumours, I have compiled the following tables, which are based upon the hospital data previously referred to.

## TABLE IX.

SHOWING THE RELATIVE FREQUENCY OF TUMOURS IN GENERAL, AS COMPARED WITH THAT OF THE CHIEF LOCAL VARIETIES, IN PERSONS OF THE TWO SEXES COMBINED.

| Kind of Neoplasm. | Neoplasms in General. | Digestive System. | Stomach. | Skin. | Tongue and Mouth. | Rectum. | Lower Lip. |
|---|---|---|---|---|---|---|---|
| | Per Cent. | Per Cent. | Per Cent. | Per Cent. | Per Cent. | Per Cent. | Per Cent. |
| Epithelioma .. | 54·5 | 93·2 | 100 | 42·7 | 91·36 | 85·87 | 94·32 |
| Sarcoma .. | 9·4 | 1·6 | — | 1·3 | 1·70 | 1·50 | 1·13 |
| Non-malignant neoplasms .. | 24·7 | 4·0 | — | 12·4 | 3·87 | 12·63 | 4·26 |
| Cysts .. | 11·4 | 1·2 | — | 33·6 | 3·07 | — | 0·29 |

## TABLE X.

SHOWING THE RELATIVE FREQUENCY OF TUMOURS IN GENERAL IN PERSONS OF THE FEMALE SEX, AS COMPARED WITH THAT OF THE CHIEF LOCAL VARIETIES IN FEMALES.

| Kind of Neoplasm. | Female Neoplasms in General. | Digestive System. | Uterine Neoplasms. | Breast Neoplasms. | Tongue and Mouth. | Skin Neoplasms in Females. | Ovarian Neoplasms. |
|---|---|---|---|---|---|---|---|
| | Per Cent. | Per Cent. | Per Cent. | Per Cent. | Per Cent. | Per Cent. | Per Cent. |
| Epithelioma .. | 48·7 | 87·4 | 59·30 | 77·7 | 67·79 | 34·1 | 3·36 |
| Sarcoma .. | 6·3 | 2·3 | 0·08 | 3·9 | 6·04 | 1·8 | 2·96 |
| Non-malignant neoplasms .. | 33·4 | 7·3 | 40·54 | 15·7 | 12·75 | 29·1 | 0·12 |
| Cysts .. | 11·6 | 3·0 | 0·08 | 2·7 | 13·42 | 35·0 | 93·54 |

## TABLE XI.

SHOWING THE RELATIVE FREQUENCY OF TUMOURS IN GENERAL IN PERSONS OF THE MALE SEX, AS COMPARED WITH THAT OF THE CHIEF LOCAL VARIETIES IN MALES.

| Kind of Neoplasm. | Male Neoplasms. | Digestive System. | Skin. | Lower Lip. | Tongue and Mouth. | Rectum. | Testicle. |
|---|---|---|---|---|---|---|---|
| | Per Cent. | Per Cent. | Per Cent. | Per Cent. | Per Cent. | Per Cent. | Per Cent. |
| Epithelioma .. | 55·1 | 95·5 | 48·94 | 97·03 | 96·17 | 86·15 | 29·04 |
| Sarcoma .. | 13·6 | 1·4 | 0·92 | 0·60 | 0·82 | 2·16 | 44·09 |
| Non-malignant neoplasms .. | 22·7 | 2·6 | 17·47 | 2·37 | 2·05 | 11·69 | 1·07 |
| Cysts .. | 8·6 | 0·5 | 32·67 | — | 0·96 | — | 25·80 |

These data show that the liability of the different organs to evolve the various tumours is extraordinarily variable. Thus, while in some parts of the body certain tumours hardly ever arise, these same parts, nevertheless, often originate other tumours, although the latter are of the rarest occurrence in yet other parts.

Thus, the digestive system as a whole, as well as each of its chief component organs (stomach, liver, rectum, intestines etc.), manifests extraordinary proclivity to epithelioma in both sexes; while, as regards sarcoma, non-malignant tumours, and cysts, there is comparative immunity. This fact, in conjunction with others of similar import, seems to point to the digestive system as being in some way, specially concerned in the causation of epithelial cancer.

Although the proneness of the uterus to epithelioma, as compared with its proneness to other tumours, is above the average for females in general, yet it is much surpassed in this respect by the stomach, rectum, mamma and tongue.

By way of contrast with the foregoing, it may be pointed out that the relative liability of the skin to epithelial cancer, is decidedly below the average; while that of the ovaries is quite insignificant.

In all of the above-mentioned organs, the proclivity to sarcoma is decidedly below the average; although the relative frequency of its occurrence *inter se*, presents considerable variations.

In the uterus, stomach, and skin, for instance, sarcoma is remarkably rare. Whereas, in the female breast, ovaries and rectum, rather more cases are met with; but, of all the organs included in these tables, only the testis manifests great relative proneness to sarcoma.

The most striking feature in the neoplastic pathogeny of the uterus is not its proclivity to cancer, but its great relative proneness to non-malignant tumours (myoma); with this, the almost complete immunity of the stomach, intestines and ovaries from such tumours, contrasts markedly.

Indeed, so great is the relative frequency of epithelioma of the stomach, as compared with its liability to non-malignant tumours and cysts; that, for practical purposes, the very existence of these latter may be ignored.

Again, while the relative proneness of the uterus, stomach and intestines to originate cysts is infinitesimal; yet, tumours of this kind arise in the ovaries, with such preponderating frequency, as to reduce the ratio of all other ovarian tumours to insignificant proportions.

In every part of the body where tumours arise, we meet with similar phenomena.

These extraordinary differences in morbid proclivity, are among the most remarkable facts in the whole range of neoplastic pathogeny; and no doubt the solution of the problem of the origin of tumours, concentres in them.

It seems to me impossible to account for such vagaries, otherwise than as the result of biological peculiarities inherent in the various tissues of the affected parts; and in their concomitant developmental and structural diversities, all of which are ultimately ascribable to functional modifications.

No doubt in every such locality there must be corresponding morphological changes, although the microscope has hitherto failed adequately to reveal them.

It is thus evident, that the influence of locality in determining the genesis, structure, and qualities of tumours, is very great.

In concluding this chapter, I append tables giving details of my analysis of 15,481 consecutive primary tumours, as met with in metropolitan hospital patients, which will I think be useful for reference purposes.

# TABLE XII.

SHOWING THE INITIAL SEATS OF TUMOURS AND THEIR RELATIVE FREQUENCY IN BOTH SEXES

| Seat. | Epithelioma (*vel* Carcinoma). | Sarcoma. | Fibroma. | Lipoma. | Adenoma. | Papilloma. | Osteoma. | Chondroma. | Angioma. | Cystoma. | Miscellaneous. | Total. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Uterus | 1571 | 2 | 1073 [1] | — | 1 | — | — | — | — | 2 | — | 2649 |
| Breast | 1879 | 99 [2] | 1 [3] | 2 | 372 | 3 | — | 1 | 1 | 64 | — | 2422 |
| Skin | 559 | 17 | 16 | — | 3 [4] | 98 | — | — | 140 | 440 [5] | 36 [6] | 1309 |
| Connective tissue | — | 330 [7] | 98 | 558 | — | — | — | — | — | 85 | — | 1071 |
| Tongue and mouth | 804 | 15 [8] | 3 [9] | — | 4 [10] | 19 [11] | — | — | 8 | 27 [12] | — | 880 |
| Ovary | 27 | 24 | 1 | — | — | — | — | — | — | 752 [13] | — | 804 |
| External genitals | 340 | 3 | 19 | 1 | — | 208 [14] | — | — | — | 141 | — | 712 |
| Bones (*ex* maxillæ) | 14 | 236 [15] | 15 | — | — | — | 256 | 35 | — | 1 | — | 557 |
| Rectum | 401 | 7 | 1 | — | 52 | 6 | — | — | — | — | — | 467 |
| Maxilla { Superior / Inferior | 70 / 13 | 102 / 48 | 136 [16] | — | — | — | 3 / 2 | 2 / 1 | — | 29 | — | 406 |
| Stomach | 352 | — | — | — | — | — | — | — | — | — | — | 352 |
| Lip | 332 | 4 | 1 | — | — | 8 | — | — | 6 | 1 | — | 352 |
| Brain | 1 | 1 | — | — | — | — | — | — | — | 1 | 287 [17] | 290 |
| Liver | 228 | — | — | — | — | — | — | — | — | 1 | — | 229 |
| Œsophagus | 179 | — | — | — | — | — | — | — | — | — | — | 179 |
| Parotid | 2 | 36 [18] | — | — | 64 [19] | — | — | 27 | — | 7 | — | 136 |
| Mediastinum | 15 | 11 | — | — | — | — | — | 1 | — | — | 107 | 134 |
| Intestine (*ex* rectum and anus) | 98 | 1 [20] | — | — | — | — | — | — | — | — | — | 99 |
| Testis | 27 | 41 [21] | — | — | — | — | — | 1 | — | 24 | — | 93 |
| Bladder | 59 | 6 | 2 | — | — | 23 | — | — | — | — | — | 90 |
| Nasal fossæ | — | 1 | 78 [22] | — | 1 | — | — | — | — | — | — | 80 |
| Lymphatic glands | 59 | 12 | — | — | — | — | — | — | — | — | — | 71 |
| Peritoneum | 54 | 11 | — | — | — | — | — | — | — | 3 | — | 68 |
| Larynx | 38 | 2 | 6 | — | — | 13 | — | — | — | — | — | 59 |
| Eye | 1 | 40 | 2 | — | — | 1 | — | — | 1 | — | — | 45 |
| Ear (external) | 13 | 1 [23] | 19 [24] | — | — | 2 | — | 1 | 1 | — | — | 37 |
| Kidney | 24 | 8 | — | — | — | — | — | — | — | 2 | — | 34 |
| Anus | 27 | — | — | — | — | 2 [25] | — | — | — | — | — | 29 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Thyroid .. .. .. .. | 7 | 1 | — | — | — | — | — | — | — | 15 | — | 23 |
| Pancreas .. .. .. .. | 21 | — | — | — | — | — | — | — | — | — | — | 21 |
| Tonsil .. .. .. .. | 13 | 5 | — | — | — | — | — | — | — | — | — | 18 |
| Lung .. .. .. .. | 14 | 3 | — | — | — | — | — | — | — | — | — | 17 |
| Submaxillary gland .. .. | 4 | 4 | — | — | 5 | — | — | 2 | — | 2 | — | 17 |
| Pharynx .. .. .. .. | 14 | 2 | — | — | — | — | — | — | — | — | — | 16 |
| Pelvis .. .. .. .. | 10 | 4 [26] | — | — | — | — | — | — | — | 1 | — | 15 |
| Gall-bladder .. .. .. | 11 | — | — | — | — | — | — | — | — | — | — | 11 |
| Prostate .. .. .. .. | 7 | 2 | — | — | — | — | — | — | — | — | — | 9 |
| Spinal cord .. .. .. | — | 1 | — | — | — | — | — | — | — | — | 6 | 7 |
| Urethra .. .. .. .. | 1 | — | — | — | — | 2 | — | — | — | — | — | 3 |
| Pleura .. .. .. .. | 3 | — | — | — | — | — | — | — | — | — | — | 3 |
| Trachea .. .. .. .. | — | — | 1 | — | — | 1 | — | — | — | — | — | 2 |
| Pericardium .. .. .. | 2 | — | — | — | — | — | — | — | — | — | — | 2 |
| Lachrymal gland .. .. .. | — | — | — | — | 1 | — | — | 1 | — | — | — | 2 |
| Spleen .. .. .. .. | 1 | — | — | — | — | — | — | — | — | — | — | 1 |
| Supra-renal body .. .. .. | — | 1 | — | — | — | — | — | — | — | — | — | 1 |
| Coccygeal gland .. .. .. | 1 | — | — | — | — | — | — | — | — | — | — | 1 |
| Abdominal wall (not skin) .. | 1 | — | — | — | — | — | — | — | — | — | — | 1 |
| Heart .. .. .. .. | — | — | 1 | — | — | — | — | — | — | — | — | 1 |
| Total .. .. .. | 7297 | 1081 | 1473 | 560 | 503 | 386 | 261 | 72 | 157 | 1598 | 436 | 13,824 |
| Unclassified .. .. | 581 | 269 | 188 | 1 | 2 | — | — | 9 | — | 42 | 565 | 1657 |
| Grand total .. .. | 7878 | 1350 | 1661 | 561 | 505 | 386 | 261 | 81 | 157 | 1640 | 1001 | 15,481 |

1 Myo-fibroma, 883; myxo-fibroma (polypoid), 190.
2 Myxoma, 4.
3 The fibro-adenomas are classed with the adenomas.
4 Of sweat-glands.
5 Sebaceous.
6 Moles.
7 Myxoma, 22.
8 Palate, 12; tongue, 1; mouth, 1; myxoma, 1.
9 Palate, 2; tongue, 1.
10 Palate.
11 Tongue, 8; palate, 5; mouth, 5; gum, 1.
12 Ranula, 22; dermoid, 5.
13 Ovarian, 635; broad ligament, 87; dermoid, 30.
14 Non-venereal.
15 Myxoma, 1.
16 Epulis, 130.
17 Cerebral, 248; cerebellar, 39.
18 Myxoma, 4.
19 The fibro-adenomas are classed with the adenomas
20 Colon.
21 Myxoma, 1.
22 Polypoid myxo-fibromas.
23 Melanotic.
24 Aural polypi, 14.
25 Non-venereal.
26 Myxoma, 1

# TABLE XIII.

SHOWING THE INITIAL SEATS OF TUMOURS AND THEIR RELATIVE FREQUENCY IN MALES.

| Seat. | Epithelioma (*vel* Carcinoma). | Sarcoma. | Fibroma. | Lipoma. | Adenoma. | Papilloma. | Osteoma. | Chondroma. | Angioma. | Cystoma. | Unclassified. | Total. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Skin | 370 | 7 | 6 | — | 1[1] | 56 | — | — | 57 | 247[2] | 12[3] | 756 |
| Tongue and mouth | 703 | 6[4] | — | — | 1[5] | 11[6] | — | — | 3[7] | 7[8] | — | 731 |
| Connective tissue | — | 183[9] | 28 | 172 | — | — | — | — | — | 50 | — | 433 |
| Lip | 327[10] | 2[11] | — | — | — | 4 | — | — | 4[12] | — | — | 337 |
| External genitals | 182[13] | — | 2 | — | — | 31[14] | — | — | — | 67[15] | — | 282 |
| Bones (*ex* maxillæ) | 7 | 134[16] | 8[17] | — | — | — | 114 | 17 | — | 1 | — | 281 |
| Rectum | 199 | 5 | 1 | — | 26 | — | — | — | — | ... | — | 231 |
| Stomach | 222 | — | — | — | — | — | — | — | — | — | — | 222 |
| Maxilla { Superior | 42 | 53 } | 20[18] | — | — | — | { 2 | 1 } | — | 17 | — | 180 |
| Maxilla { Inferior | 12 | 31 } | | | | | { 1 | 1 } | | | | |
| Brain | — | 1 | — | — | — | — | — | — | — | 1 | 157[19] | 159 |
| Œsophagus | 144 | — | — | — | — | — | — | — | — | — | — | 144 |
| Liver | 115 | — | — | — | — | — | — | — | — | — | — | 115 |
| Testis | 27 | 41[20] | — | — | — | — | — | 1 | — | 24 | — | 93 |
| Mediastinum | 11 | 7 | — | — | — | — | — | — | — | — | 73 | 91 |
| Bladder | 43 | 5 | 1 | — | — | 21 | — | — | — | — | — | 70 |
| Parotid | 2 | 18[21] | — | — | 26 | — | — | 14 | — | 3 | — | 63 |
| Intestine (*ex* rectum and anus) | 49 | 1[22] | — | — | — | — | — | — | — | — | — | 50 |
| Larynx | 34 | 2 | 4 | — | — | 9 | — | — | — | — | — | 49 |
| Lymphatic glands | 33 | 10 | — | — | — | — | — | — | — | — | — | 43 |
| Nasal fossæ | — | 1 | 31[23] | — | 1 | — | — | — | — | — | — | 33 |
| Peritoneum | 20 | 8 | — | — | — | — | — | — | — | 1 | — | 29 |
| Breast | 16 | 5[24] | — | 1 | 1 | — | — | — | 1 | 1 | — | 25 |
| Kidney | 17 | 3 | — | — | — | — | — | — | — | 1 | — | 21 |
| Eye | — | 20 | 1 | — | — | — | — | — | — | — | — | 21 |
| Ear (external) | 11 | 1[25] | 6[26] | — | — | 2 | — | — | — | — | — | 20 |
| Anus | 17 | — | — | — | — | 1 | — | — | — | — | — | 18 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pancreas .. .. .. .. | 14 | — | — | — | — | — | — | — | — | — | — | 14 |
| Tonsil .. .. .. .. | 9 | 5 | — | — | — | — | — | — | — | — | — | 14 |
| Lung .. .. .. .. | 10 | 3 | — | — | — | — | — | — | — | — | — | 13 |
| Thyroid .. .. .. .. | 4 | — | — | — | — | — | — | — | — | 9 | — | 13 |
| Submaxillary gland .. .. | 4 | 4 | — | — | 1 | — | — | 1 | — | 2 | — | 12 |
| Prostate .. .. .. .. | 7 | 2 | — | — | — | — | — | — | — | — | — | 9 |
| Pharynx .. .. .. .. | 7 | — | — | — | — | — | — | — | — | — | — | 7 |
| Gall bladder .. .. .. | 5 | — | — | — | — | — | — | — | — | — | — | 5 |
| Urethra .. .. .. .. | 1 | — | — | — | — | 2 | — | — | — | — | — | 3 |
| Spinal cord .. .. .. | — | — | — | — | — | — | — | — | — | — | 3 | 3 |
| Pelvis .. .. .. .. | 1 | — | — | — | — | — | — | — | — | — | — | 1 |
| Pericardium .. .. .. | 1 | — | — | — | — | — | — | — | — | — | — | 1 |
| Spleen .. .. .. .. | 1 | — | — | — | — | — | — | — | — | — | — | 1 |
| Lachrymal gland .. .. .. | — | — | — | — | — | — | — | 1 | — | — | — | 1 |
| Supra-renal capsule .. .. | — | 1 | — | — | — | — | — | — | — | — | — | 1 |
| Coccygeal gland .. .. .. | 1 | — | — | — | — | — | — | — | — | — | — | 1 |
| Abdominal wall (not skin) .. | 1 | — | — | — | — | — | — | — | — | — | — | 1 |
| Heart .. .. .. .. | — | — | 1 | — | — | — | — | — | — | — | — | 1 |
| Total .. .. .. | 2669 | 559 | 109 | 172 | 57 | 137 | 117 | 36 | 65 | 431 | 245 | 4597 |
| Unclassified .. .. | 192 | 143 | 67 | 1 | 1 | — | — | 5 | — | 18 | 167 | 594 |
| Grand total .. .. | 2861 | 702 | 176 | 173 | 58 | 137 | 117 | 41 | 65 | 449 | 412 | 5191 |

1 Of cutaneous sweat-gland.
2 Sebaceous.
3 Moles.
4 Tongue, 1 ; mouth, 1 ; palate, 4.
5 Palate.
6 Tongue, 5 ; soft palate, 3 ; roof of mouth, 2 ; gum, 1.
7 Tongue, 1 ; mouth, 2.
8 Ranula, 6 ; dermoid, 1.
9 Myxoma, 14.
10 Upper lip, 1.
11 Both of upper lip.
12 Lower, 3 ; upper, 1.
13 Penis, 106 ; scrotum, 76.
14 Non-venereal.
15 Spermatic cord, 66 ; dermoid of scrotum, 1.
16 Myxoma, 1.
17 Basis cranii-nasophgl. polypi.
18 Epulis.
19 Cerebral, 135 ; cerebellar, 22.
20 Myxoma, 1.
21 Myxoma, 3.
22 Colon.
23 Polypoid myxo-fibromas.
24 Myxoma, 2.
25 Melanotic.
26 Aural polypus, 1.

# TABLE XIV.

[SHOWING THE INITIAL SEATS OF TUMOURS AND THEIR RELATIVE FREQUENCY IN FEMALES.

| Seat. | Epithelioma (*vel* Carcinoma). | Sarcoma. | Fibroma. | Lipoma. | Adenoma. | Papilloma. | Osteoma. | Chondroma. | Angioma. | Cystoma. | Unclassified. | Total. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Uterus .. .. .. .. | 1571 | 2 | 1073 [1] | — | 1 | — | — | — | — | 2 | — | 2649 |
| Breast .. .. .. .. | 1863 | 94 [2] | 1 [3] | 1 | 371 | 3 | — | 1 | — | 63 | — | 2397 |
| Ovary .. .. .. .. | 27 | 24 | 1 | — | — | — | — | — | — | 752 [4] | — | 804 |
| Connective tissue .. .. .. | — | 147 [5] | 70 | 386 | — | — | — | — | — | 35 | — | 638 |
| Skin .. .. .. .. | 189 | 10 | 10 | — | 2 [6] | 42 | — | — | 83 | 193 [7] | 24 [8] | 553 |
| External genitals .. .. .. | 158 [9] | 3 [10] | 17 [11] | 1 | — | 177 [12] | — | — | — | 74 [13] | — | 430 |
| Bones (*ex* maxillæ) .. .. | 7 | 102 | 7 [14] | — | — | — | 142 | 18 | — | — | — | 276 |
| Rectum .. .. .. .. | 202 | 2 | — | — | 26 [15] | 6 | — | — | — | — | — | 236 |
| Maxilla { Superior .. .. | 28 | 49 | 116 [16] | — | — | — | 1 | 1 | — | 12 | — | 226 |
| Maxilla { Inferior .. .. | 1 | 17 | | | | | 1 | — | | | | |
| Tongue and mouth .. .. | 101 | 9 [17] | 3 [18] | — | 3 [19] | 8 [20] | — | — | 5 | 20 [21] | — | 149 |
| Brain .. .. .. .. | 1 [22] | — | — | — | — | — | — | — | — | — | 130 [23] | 131 |
| Stomach .. .. .. .. | 130 | — | — | — | — | — | — | — | — | — | — | 130 |
| Liver .. .. .. .. | 113 | — | — | — | — | — | — | — | — | 1 | — | 114 |
| Parotid .. .. .. .. | — | 18 [24] | — | — | 38 [25] | — | — | 13 | — | 4 | — | 73 |
| Intestine (*ex* rectum and anus) .. | 49 | — | — | — | — | — | — | — | — | — | — | 49 |
| Nasal fossæ .. .. .. | — | — | 47 [26] | — | — | — | — | — | — | — | — | 47 |
| Mediastinum .. .. .. | 4 | 4 | — | — | — | — | — | 1 | — | — | 34 | 43 |
| Peritoneum .. .. .. | 34 | 3 | — | — | — | — | — | — | — | 2 | — | 39 |
| Œsophagus .. .. .. | 35 | — | — | — | — | — | — | — | — | — | — | 35 |
| Lymphatic glands .. .. | 26 | 2 | — | — | — | — | — | — | — | — | — | 28 |
| Eye .. .. .. .. | 1 | 20 | 1 | — | — | 1 | — | — | 1 | — | — | 24 |
| Bladder .. .. .. .. | 16 | 1 | 1 | — | — | 2 | — | — | — | — | — | 20 |
| Ear (external) .. .. .. | 2 | — | 13 [27] | — | — | — | — | 1 | 1 | — | — | 17 |
| Lip .. .. .. .. .. | 5 [28] | 2 [29] | 1 [30] | — | — | 4 [31] | — | — | 2 [32] | 1 | — | 15 |
| Pelvis .. .. .. .. | 9 | 4 [33] | — | — | — | — | — | — | — | 1 | — | 14 |
| Kidney .. .. .. .. | 7 | 5 | — | — | — | — | — | — | — | 1 | — | 13 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Anus .. .. .. .. | 10 | — | — | — | — | 1 [34] | — | — | — | — | — | 11 |
| Larynx .. .. .. .. | 4 | — | 2 | — | — | 4 | — | — | — | — | — | 10 |
| Thyroid .. .. .. .. | 3 | 1 | — | — | — | — | — | — | — | 6 | — | 10 |
| Pharynx .. .. .. .. | 7 | 2 | — | — | — | — | — | — | — | — | — | 9 |
| Pancreas .. .. .. .. | 7 | — | — | — | — | — | — | — | — | — | — | 7 |
| Gall-bladder .. .. .. | 6 | — | — | — | — | — | — | — | — | — | — | 6 |
| Submaxillary gland .. .. | — | — | — | — | 4 | — | — | 1 | — | — | — | 5 |
| Spinal cord .. .. .. | — | 1 | — | — | — | — | — | — | — | — | 3 | 4 |
| Lung .. .. .. .. | 4 | — | — | — | — | — | — | — | — | — | — | 4 |
| Tonsil .. .. .. .. | 4 | — | — | — | — | — | — | — | — | — | — | 4 |
| Pleura .. .. .. .. | 3 | — | — | — | — | — | — | — | — | — | — | 3 |
| Trachea .. .. .. .. | — | — | 1 | — | — | 1 | — | — | — | — | — | 2 |
| Lachrymal gland .. .. .. | — | — | — | — | 1 | — | — | — | — | — | — | 1 |
| Pericardium .. .. .. | 1 | — | — | — | — | — | — | — | — | — | — | 1 |
| Total .. .. .. | 4628 | 522 | 1364 | 388 | 446 | 249 | 144 | 36 | 92 | 1167 | 191 | 9227 |
| Unclassified .. .. | 389 | 126 | 121 | — | 1 | — | — | 4 | — | 24 | 398 | 1063 |
| Grand total .. .. | 5017 | 648 | 1485 | 388 | 447 | 249 | 144 | 40 | 92 | 1191 | 589 | 10,290 |

1 Myo-fibroma, 883 ; myxoma-fibroma (polypoid), 190.
2 Myxoma, 2.
3 The fibro-adenomas are classed with the adenomas.
4 Ovarian, 635 ; broad ligament, 87 ; dermoid, 30.
5 Myxoma, 8.
6 Cutaneous sweat-glands.
7 Sebaceous.
8 Moles.
9 Vulva, 104 ; nympha, 6 ; clitoris, 7 ; symphysis [pubis, 1 ; vagina, 40.
10 Vagina, 2 ; vulva, 1.
11 Labia major, 12 ; labia minor, 2 ; vagina, 3.
12 Urethral caruncle, 148 ; the others non-venereal.
13 External genitals, 61 ; round ligament, 13.
14 Basis cranii.
15 Polypoid.
16 Epulis, 110.
17 Palate, 8 ; myxoma, 1.
18 Palate, 2 ; tongue, 1.
19 Palate.
20 Tongue, 3 ; soft palate, 1 ; uvula, 4.
21 Ranula, 16 ; dermoid, 4.
22 Dura mater.
23 Cerebral, 113 ; cerebellar, 17.
24 Myxoma, 1.
25 The fibro-adenomas are classed with the adenomas.
26 Polypoid myxo-fibroma.
27 Aural polypi.
28 Lower lip, 3 ; upper lip, 2.
29 Upper lip, 2.
30 Lower lip.
31 Upper lip, 1.
32 Upper lip, 2.
33 Myxoma, 1.
34 Non-venereal.

# CHAPTER XIX

## THE MORPHOLOGY OF MALIGNANT TUMOURS

Inasmuch as every part of the body is liable to its own peculiar forms of cancerous growth; and since the diverse characters manifested by each variety, according to its seat of origin, show that the influence of the locality in determining the structure and progress of the disease is very great: it is evident that no study of the life-history of neoplastic processes can be complete, which ignores pre-existing structural peculiarities.

We must bear in mind, that tumour-products are never of such a monstrous nature, as not to present some analogy with the normal structure of the part whence they may originate, either in its embryonic or post-embryonic state. It is to be regretted that modern pathologists, in their eager pursuit of microbes and specific causative agents, have so far neglected this important consideration; that the links connecting these extremes have, for the most part, still to be ascertained.

### The Primary Tumour.

In a previous chapter,[1] I have adduced facts to prove that the matrix of a malignant tumour is generally a redundant formation of pre-natal origin, structurally and functionally uncombined with the part of the body in which it exists, although generally a remote derivative thereof. In this respect, malignant and non-malignant tumours are similarly conditioned; that is to say, their matrix is usually the outcome of *vitium primæ formationis.*

There are, however, reasons for believing,[2] that malignant and other tumours may exceptionally arise from a matrix of post-natal origin, owing to the detachment of proliferous tissue elements, in consequence of injury or disease. In the latter, as in the former case, however, the tumour matrix is separate and distinct from the local tissues, in which it is embedded.

The initial lesion of cancer is generally solitary; and, so exceedingly minute, that its original germ is probably but a single one of the constituent cells of the matrix, or a small cellular group.

This supposition accords with what we know as to the origin of secondary cancers; for, the capillaries through which the germs of such tumours must have passed are often so minute, as not to admit of the passage of more than a single cell. Thus, the primordial starting-point

[1] Chapter VII. [2] Chapter XI.

of every tumour, as of every organ of the body, is in all probability a single cell.

In its growth, as in its genesis, the cancerous new formation also mimics the corresponding normal structure whence its matrix was originally derived; although it never attains to the structural or functional perfection of the physiological prototype. The cancerous growth is, in fact, the result of a modified, superinduced repetition of a certain portion of the ontogeny of this prototype. As Broca has well said: "Dans l'ensemble c'est un excês de formation; dans les détails c'est un arrêt de développement."

In the case of non-malignant tumours this mimicry is generally so complete, that the tumour structure is commonly an almost exact replica of its physiological prototype; indeed, certain tumours of this kind[1] can hardly be distinguished from anomalies *per excessum.*

Between these extremes, we meet with numerous intermediate forms.

In consequence of this peculiarity, the anatomical features of malignant tumours are very varied, according to the nature of the matrix whence they originate; in this way, the differences between malignant epithelial and connective-tissue tumours may be explained; as also the diverse structural varieties of tumours, comprised within the limits of each of these types.

Thus, malignant tumours of epithelial origin increase in size, by the growth of solid bud-like processes of proliferous epithelial cells; which, as they augment, grow and ramify in the adjacent tissues, mimicking the ontogenesis of their physiological prototype. By the repetition and centrifugal extension of this process, the cancerous tumour is formed; and this crude growth tends to reproduce itself indefinitely.

Along with it, however, there also goes a certain amount of organization of the growing mass, with manifest tendency to reproduce structural features characteristic of the physiological prototype; hence the very marked morphological difference between cancers of various parts. What, for instance, can be more divergent in this respect, than the morphological appearances of representative cancers from such different parts as the skin, stomach, rectum, uterus and breast?[2]

The microscopical examination of such tumours shows, that they are sufficiently organized to present unmistakable histological resemblance, to the structures whence they originate. And with this morphological differentiation certain corresponding, but less obvious, physiological diversities may also be detected, as I have previously mentioned.

Herein malignant tumours differ from inflammatory pseudo-plasms, which everywhere tend to reproduce the same granulomatous structure.

Although we know from histology the infiltrating character of such growths, yet, to the unaided senses, these tumours generally present as more or less circumscribed masses. On careful examination of their

[1] *E.g.*, Angiomata, moles, lipomata, subungual exostoses, etc. (*q.v.* an essay by the author in *Bristol Medico-Chirurgical Journal*, March, 1904, p. 17).

[2] For histological details reference may be made to the author's previous publications—viz., "Diseases of the Breast," p. 151 *et seq.*; "Uterine Tumours," pp. 31 and 199; also "Twentieth-Century Practice of Medicine," vol. xvii., pp. 310, 486, etc.

periphery, it will be seen that the passage from the diseased to the healthy tissue is by no means sharply defined, the irregularly growing edge of the cancer dovetailing, as it were, into the surrounding pre-existing tissues.

Of all malignant tumours, the sarcomas are the most circumscribed, some forms having a pseudo-capsule; yet, notwithstanding this, processes of the disease nearly always spread out into the surrounding tissues, far beyond the apparent limits of the tumour.

Taken in their entirety, the cancerous cells form branching, racemose masses, ingrowing into the surrounding structures.

By serial sections, after the manner adopted by embryologists, Hauser and others have demonstrated, that the appearance of closed alveoli full of cells, revealed by the microscopical examination of sections of epitheliomatous tumours, is really deceptive; the spaces which appear to be such, are really nothing more than sections of branching epithelial ingrowths, directly continuous with the rest of the tumour parenchyma.

The effect of cancerous growths on the tissues in the midst of which they evolve, is to cause their destruction by "pressure atrophy"; if, indeed, such a term can properly be applied to a process, which is probably due to a special kind of metabolism, such as is often seen in various phases of ontogeny.

If we examine the growing edge of a cancerous tumour, we shall find that the disease progresses by the continuous centrifugal extension of its ingrowing epithelial processes. These spread most rapidly in the directions of least resistance, which are usually the adjacent lymphatics, peri-vascular sheaths and small veins. As these become distended with cancer cells, fine, elongated, cord-like processes of cancerous growth are formed, which often extend from the parent tumour far into the surrounding tissues. In this connexion nodular growths may develop which, to the naked eye, appear to have no connexion with the primary tumour. In their subsequent progress, these secondary formations behave exactly as the primary growth. Thus, as the disease extends, the parent tumour blends with the outlying nodules, forming a diffused mass of infiltrating growth.

In referring to this infiltrating characteristic of cancer, Astley Cooper [1] says, when describing mammary cancer:—"I would observe that the scirrhous tumour is not all of the disease; there are roots which extend to a considerable distance; and those who gave the disease the name of "cancer," probably knew more of its nature than we are disposed to give them credit for. It is supposed by some, that this name was given on account of the appearance of the surrounding veins. I should rather say it was from the appearances on dissection, than from anything without. When you dissect a scirrhous tumour, you see a number of roots proceeding to a considerable distance; and, if you remove the tumour only, and not the roots, there will be little advantage from the operation: no glandular structure, nor any of the roots, should be allowed to remain."

[1] "Lectures on Surgery," 1839, p. 386.

This admirable summary of the subject, is entirely in accord with the results of modern research.

It will be gathered from what has been stated, that the integration of cancerous growths is very inferior to that of normal parts. New centres of development are constantly arising among their constituent proliferating cells; so that, before the initial growth has made much progress, numerous subsidiary centres of morbid activity have arisen in it, or in its vicinity.

The physical characters of cancerous tumours are determined by the structure of the part wherein they originate; hence, hard cancers ("*scirrhous*") are the dominant forms that arise from parts rich in fibrous tissue, such as the mamma and skin; while, in the uterus, stomach and rectum, where fibrillar tissue is scanty, soft, succulent or fragile forms of cancer predominate.

The shape and size of the constituent cells of cancerous tumours, and their grouping, vary according to the locality; but some resemblance is always noticeable, in these respects, between the pathological new formation and its physiological prototype.

Thus Johannes Müller,[1] more than half a century ago, demonstrated the presence of casein in breast cancers; and the abundance of fatty matters, contained in the cells of such neoplasms, is well known. We are thus reminded of the similar metamorphoses, that the cells of the normal gland undergo during lactation; but, the nearest approach to normal secretion that the pathological structure ever produces, is a scanty, mucoid fluid, not unlike a very poor kind of colostrum.

In comparatively recent times, Waring[2] has demonstrated the important fact, that the constituent cells of cancers of the stomach and pancreas, produce the same ferments—pepsin, trypsin etc.—as the normal secretory cells of these organs.

If, then, the secretions elaborated by cancerous new formations, fall far short of those produced by their corresponding anatomical prototypes, we may unhesitatingly ascribe this deficiency to the fact; that secretory cells tend to lose their normal functional aptitudes, when in a state of active proliferation, as the experiments of Martinotti and others have shown.

The essential factor underlying the increase of cancerous tumours is, the continuous growth and proliferation of their constituent cellular elements. The pathological cells multiply, like their physiological prototypes, chiefly by indirect nuclear division; and the similarity extends even to the details of karyokinesis—equatorial plates, achromatic spindles etc.[3] Thus, the component cells of a cancerous tumour, are the direct descendants of the primary neoplastic cells.

In studying pathological neoplasia, much importance attaches to the nucleus and nuclear changes, for recent biological research indicates,

[1] "Über den feineren Bau und die Formen der krankhaften Geschwülste," 1838.

[2] *Journal of Anatomy*, etc., October, 1893, p. 142: "The Physiological Characters of Carcinomata."

[3] Cattle and others think, considering the comparatively sparse occurrence of mitotic figures in the actively growing zone of many cancers, that direct division of the cells (a-mitosis) is common" (*Journal of Pathology*, etc., February, 1894).

that the nucleus is specially concerned in regulating the growth and multiplication of cells.

The nuclei of cancer cells are larger, richer in chromatin, and they more frequently originate karyokinetic figures, than their physiological prototypes. More than a single nucleus is commonly present; and the nuclei often shed their chromatin into the surrounding protoplasm, as a sort of preliminary to division, whereby the so-called "giant cells" of cancer arise. Hypo- and hyper-chromatic conditions of the nucleus are frequently met with.[1]

Asymmetrical and multipolar mitoses also occur with undue frequency; and the axis of cellular division is often displaced from its normal plane, as was first pointed out by Fabre-Domergue. Moreover, abortive mitoses are not uncommon. Nuclear fragments detached during mitotic changes, probably originate the "corps colorables" described by Foà and others. Such conditions are most marked, where the disease is in active progress.

It was formerly thought that changes of this kind were specially characteristic of cancer; but it is now known that similar conditions are met with in various inflammatory processes, and even in non-malignant tumours. Thus, although the mitoses of cancer are extraordinarily variable, no new types are produced.

In the processes of repair and regeneration after wounds, similar changes are noticeable; as well as in the various transplantation experiments with epithelial tissues, and especially in Loeb's cultures of epidermis in blood-serum and agar, as previously mentioned.[2]

Pierallini[3] and D'Arcy Power,[4] by means of various forms of artificial stimulation (heat, electricity, traumata etc.), succeeded in reproducing these conditions experimentally; while Galeotti[5] has shown, by treating proliferous cells with solutions of various poisons and chemical reagents etc., that these mitotic irregularities may be artificially produced in this way also.

Taken in their entirety, these deviations from the normal are but the morphological expressions of a high degree of reproductive activity, which is an essential characteristic of cancer cells.

This phenomenon seems to me to be of the same nature—in exaggerated degree—as the accelerated proliferation of epithelial cells noticeable in the processes of repair and regeneration. Just as this exceeds the physiological rate of increase requisite to maintain the normal status, so the former exceeds the latter; but I believe all these manifestations belong to the same order of events.

The wonderful reproductive activity of cancer cells, enables us to understand how a single such cell, may be the germ of a large tumour—even the largest. It is chiefly in this, their dynamic aspect, that cancer cells differ from normal cells. In their young state, as Klebs, Waldeyer

[1] Hansemann, *Arch. f. path. Anat.*, 1890, Bd. cxix., S. 299; *ibid.*, 1891, Bd. cxxiii., Heft 2; "Die mikroskopische Diagnose der bösartigen Geschwülste," 1902, S. 91, and "Ueber die Anaplasie der Geschwülstzellen," etc., *Arch. f. path. Anat.*, 1902, Bd. cxxix., S. 436.

[2] Chapter VIII.

[3] *Lo Sperimentale*, l., p. 37.

[4] *British Medical Journal*, 1893, vol. ii., p. 830.

[5] *Beitr. z. path. Anat.*, etc., 1893, Bd. xiv., Heft 2, S. 249; also 1897, Bd. xx., S. 192.

and others have observed, both possess contractile and locomotive properties.

Cancer cells are short-lived, for they are soon overtaken and destroyed by fatty, caseous, mucoid, hyaline and other degenerative changes; while vacuolation is of common occurrence. These and other changes in cancer cells, have been carefully studied and described by Pianese,[1] Hansemann and others.

It will be gathered from what has been stated, that cancer cells grow and multiply more rapidly than their physiological congeners; while, at the same time, their vitality is less stable and their developmental power less complete.

With regard to the occurrence of reduction of the nuclear chromosomes ("heterotypical mitosis"), as a special characteristic of cancer cells, this has been disproved by the discovery of similar changes in various processes having nothing to do with cancer; and by the artificial production of the same, by chemical stimulation etc., as mentioned in a previous chapter.[2]

In like manner, the significance of the various pseudo-parasitic bodies ("endocytes") found in cancer cells, and their vicinity, has been fully explained in Chapter X.; where reference was also made to the frequent presence in cancerous tumours, of various non-specific microbes.

Leucocytes and red blood-corpuscles have often been detected between closely approximated cancer cells, and even within them; while the invagination of one or more cells within another, has actually been seen to occur by many observers.

These appearances have been variously interpreted. By some pathologists, as previously mentioned,[3] they are regarded as evidence of conjugation, rejuvenescence, or "maturation" of the tumour cells; others have mistaken included cells of this kind for "cancer parasites"; while Ströbe, Podwyssotzki etc., maintain that they are simply signs of phagocytosis. It accords with this last interpretation, that leucocytes between and within cancer cells, are most frequently seen in inflamed areas. Under these circumstances mast cells are commonly met with. Another notable feature is that the stroma of the actively growing zone of cancerous tumours, is invariably infiltrated with numerous small, round, nucleated cells; and, as Goldmann[4] has shown, its vascularity is enormously increased.

It has been shown by Ide and others, that the physiological epithelial cells are knit together and communicate freely with their neighbours, by small bridges — *ponts intercellulaires* — in which both cell membrane and protoplasm are involved, and sometimes even nuclear filaments. It is probable that all the cells of the body, are knit together in this way.

In malignant epithelial tumours, these connecting-links between the different component cells, although not invariably lacking, are generally

[1] Ziegler's *Beitr. z. path. Anat.* (supplement), 1896; for epitome, *vide* Chapter X. of this work.

[2] Chapter IX.

[3] *Ibid.*

[4] *Deutsche med. Woch.*, 1906, No. 41; also *Lancet*, 1907, vol. ii., p. 1236.

very defective and inefficient; indeed, in many cancers, the constituent cells seem to exist completely detached from one another, immersed in an albuminous fluid, which is limited by the surrounding stroma.

This want of cohesion between their constituent cells, is probably one of the chief reasons why cancers are so prone to disseminate; and it is probably owing to conditions of this sort, that some cancers are so much more prone to disseminate than others.

In the initial stages of their growth, malignant tumours, like their corresponding physiological prototypes, are destitute of bloodvessels and nerves; it is only at a later period that their deficiencies in this respect are made good, by outgrowths from the surrounding tissues. Moreover, it is noteworthy that neither bloodvessels nor nerves are found within the cancer alveoli, any more than they are within the corresponding parts of the physiological prototype.

Besides this, the relations of tumour and prototype to the lymphatic system are very similar; thus, as De Sinety has shown, within the *membrana propria* of the normal mammary acini, there exists an imperfect lining of endothelial cells, which is probably a derivative of the lymphatic system; and Cornil and Ranvier—by injection of Prussian blue and nitrate of silver staining—have demonstrated that, in mammary cancer, the alveoli are in direct communication with the lymphatic radicles.

It is noteworthy that the endothelial cells of the latter, take no part in the cancerous process.

From the foregoing we learn, that there is nothing specific about cancer cells and structures, as was formerly believed; there is departure from the normal type of development, but no foreign structures are produced. Thus, it is chiefly on account of the greatly increased numbers of their constituent cells, of their disorderly grouping, of the comparatively imperfect degree of development attained, and of their less stable vitality, that cancerous structures differ from their normal prototypes.

This conformity is quite as marked in the case of the stroma, as in the case of the cancer cells; for this also takes after the pre-existing structure of the affected part. It has been much discussed, whether the cancer stroma is of new formation, or simply the modified pre-existing structure. It seems certain, from various considerations; but especially from the phenomena presented by the growth of secondary cancers in distant organs, and within bloodvessels, that the stroma is a new formation.

It must be borne in mind that the epithelial elements whence cancers originate, are normally in intimate contact with a layer of immature connective tissue rich in cellular elements, which is probably the source of the newly formed granulation tissue, whence the cancer stroma evolves. How otherwise can we explain the fact, that the stroma of secondary tumours is so like that of the primary one?

Ribbert and others who uphold the connective-tissue origin of cancer, maintain that proliferative changes of this kind in the sub-epithelial connective tissue, precede the morbid proliferation of the epithelial cells; and constitute, in fact, the initial cancerous change.

The cancer stroma is well provided with various cellular constituents (fusiform, stellate, and flattened forms, as well as lymphocytes, mast cells and leucocytes), in connexion with which mitotic figures may often be detected.

Within the cancer stroma, numerous small arteries, veins and capillaries ramify. The degree of vascularity of cancer in different organs is very variable ; and, even in different parts of the same tumour, similar irregularities are met with. These vessels have been injected by Goldmann,[1] Thiersch, Billroth and others ; and found to form networks, around the sprouting cancer-cell complexes. They are generally more numerous and less regular in their calibre and arrangement, than the corresponding normal bloodvessels, tortuous dilatations and small sacculations being of frequent occurrence. These lesions are occasionally so marked as to produce a telangiectasic condition. According to Quénu, the walls of the vessels are often thickened and their lumina occluded, in consequence of chronic endarteritis ; and Goldmann has noted that degeneration of the vascular walls is a prominent feature, even in early stages of the disease.

While the vascular system of cancers can be readily injected by the arteries—even the smallest—it is generally difficult to do so by the veins, the substance injected then finding its way into the circumferential venous system, instead of into that of the neoplasm. This is probably due to the frequent blocking of the veins by the growth of the neoplasm, by thrombi etc. Thus may be explained the venous engorgement, that is almost invariably associated with cancer.

Accompanying the stromal bloodvessels are numerous lymphatics, which have been injected, and their distribution studied by Schröder, van der Kolk, Krause, Rindfleisch and others. In the case of mammary epithelial cancer, as previously mentioned, their radicles are in direct communication with the alveoli ; a similar condition probably holds for other forms of cancer. This enables us to understand, the great frequency of dissemination in the lymphatic glands.

Probably one reason why sarcomas comparatively rarely disseminate in the lymph-glands, is that but few lymphatics enter into their composition ; indeed, the very existence of lymphatics in these tumours has been denied by some pathologists, but Pacinotti and others have demonstrated their presence.

Cancers have hitherto generally been regarded as nerveless ; but vaso-motor filaments accompany the stromal bloodvessels, although this is denied by Verneuil and Nepveu. H. Young,[2] who has lately investigated this subject, found nerve filaments in all kinds of malignant tumours, the fibres being with or without myeline. These nerves generally accompanied the stromal bloodvessels, and appeared to be branches of those normally existing in the invaded tissues.

The *chemical analysis* of cancerous growths—much neglected of late—has hitherto failed to reveal the presence of any specific morbid substance. Albuminous constituents predominate. Detailed analyses may be found in the works of Lebert, Walshe and J. Müller ; but I am not aware of any

[1] *Op. cit.*

[2] *Journal of Experimental Medicine*, 1897, vol. ii., No. 1.

recent publications of this kind, other than those I have previously referred to.

It has lately been shown that glycogen is invariably present; and, according to Freund, so is sugar. Glycogen is most abundant in the rapidly growing forms of the disease. In this respect, cancer elements resemble immature and rapidly growing structures in general, which are always rich in glycogen. Beneke has found an abundance of cholesterin and myelin.

According to recent observations, the juice of perfectly fresh mammary cancers is of an alkaline or neutral reaction; whereas, within a few hours after death, the reaction has become acid. In this respect cancer resembles the physiological tissues.

Blumenthal[1] and Bergell[2] find that cancers contain more albumin and less globulin than other tissues, being particularly rich in nucleo-albumin; and that cancer elements are specially susceptible to trypsinic digestion etc.; while Petry[3] claims that there is a special intra-cellular cancer ferment—*malignin*—by means of which cancers are endowed with their special qualities. According to Blumenthal, the pancreatic digestion of cancerous tissues takes a different course to that of other tissues, being arrested at the formation of intermediate chemical products, instead of going on to the usual terminal reactions.

Beard[4] maintains that the albumins of cancer are dextro-rotatory, the albumins of the normal body being levo-rotatory; but this needs confirmation.

Examining malignant tumours for enzymes, Petry found that cancerous substances readily undergo autolysis with increase of non-coagulable proteids, and the formation of leucin, tyrosin, hexon and purin bases, at the expense of the most complex coagulable proteids. This autolysis was due to the action of a proteolytic ferment, the products of which corresponded with those found by Salkowski, in autolysis of normal tissues.

It seems probable that the tissues of malignant tumours, like the normal tissues, teem with enzymes; but there is no proof that their specific qualities are in any way directly proportional to malignancy. Perhaps the most abundant and constant enzyme met with in cancers is the amylolitic, which is interesting when we recollect the richness in glycogen of these tumours. Buxton[5] found in cancerous tumours proteolytic enzymes, amylose, lipase, catalase, peroxidase and oxidase; while MacFadyean and Harden—working chiefly with mammary cancer—found invertase, maltase, amylase, proteolytic enzymes, catalase, oxidase, traces of lipase, and peroxidase, but no lactose.

Referring to these results, Buxton judiciously remarks: "The only conclusion they seem to warrant is, that a number of enzymes are commonly present in cancerous tumours, and that their amount and kind are independent of the character or malignancy of the growths, and

1 *Berlin. klin. Woch.*, 1905, xliii., S. 376.
2 *Deutsche med. Woch.*, etc., June 6, 1907.
3 *Zeits. f. physiol. Chemie*, 1899, Bd. xxvii., S. 398.
4 *New York Medical Record*, October 19, 1907.
5 *Journal of Medical Research*, 1903, vol. ix., p. 356; also *ibid.*, 1905, vol. xiii., p. 543.

are very similar to those found in the normal tissues of the same part." In short, it is evident that, until we know more about the enzymes of the normal tissues, it is impossible to arrive at any definite conclusion, as to the special significance of the enzymes of cancerous tumours.[1]

Hewlett and Brodie could find no traces of albumoses in cancerous tumours, although in cultures of pathogenic bacteria such substances abound. It should, however, be mentioned that Meyer has found splenic extracts from cancerous subjects, of double the toxicity met with in other cachectic states; and, in disintegrating cancerous tissues, Blumenthal has met with albumoses. Brodie failed to find even a trace of either chitin or cellulose in cancerous tumours, which indicates the absence of encapsuled protozoa.

Hewlett's investigations [2] show that the cells of epithelioma, sarcoma and adenoma, contain about the same amount of phosphorus, as those of the normal tissues; that there is no special distribution of iron in these tumours, their cells being neither richer nor poorer in this respect, than the ordinary tissue cells; and that the proteids of cancer, like those of other cellular organs, consist chiefly of nucleo-albumin.

Reference has previously been made to Waring's important researches, on the physiological properties of carcinomata.

As I have specially indicated in a previous chapter,[3] the presence of various heterotopic structures (*e.g.*, bone, cartilage, striped muscle etc.) in malignant tumours is an event of great interest, as indicating genetic connexion with pre-natal developmental irregularities (*vitium primæ formationis*).

Although the matrix of a cancerous tumour is not integrated with the tissues of the part in which it is embedded, yet it cannot usually be regarded as a heterotopic structure, since it is but a pre-natal derivative of the locality: consequently there is always some resemblance between such tumours and local structure.

It not uncommonly happens, however, that the matrix of a cancerous tumour at the time of its genesis, is displaced from its original *habitat*; and then we get a truly heterotopic cancer. Tumours of this type form a very interesting group, which ought to be more carefully studied, than they hitherto have been; for they throw a strong light on tumour pathogenesis.

For instance, there are on record many examples of malignant epithelial tumours arising in bones, lymph-glands and other localities, where epithelial elements are normally absent. Thus, Councilman found a nodule of cutaneous epidermoidal cancer, embedded in the osseous substance of the sternum: to account for this, we must remember that the sternum is evolved by the gradual approximation and fusion of two lateral halves; in this process, offsets of the overlying cutaneous matrix may be entangled and sequestrated; that this actually happens we know from the occurrence of dermoid cysts in this bone and its vicinity; the tumour described by Councilman, no doubt sprang from

[1] For further reference to this subject, *vide* Chapter IX.
[2] *British Medical Journal*, 1894, vol. ii., p. 190; *ibid.*, 1895, vol. ii., p. 206.
[3] Chapter VII.

one of these cutaneous "rests," which had been embedded in the substance of the bone.

In like manner, we see mammary epitheliomas and sarcomas, arising in the axilla, quite independently of the mammary gland, from mammary "rests" of pre-natal origin, of which I know of many examples; and the origin of epidermoidal cancers, from the mucosa of the corpus uteri, is of similar import.

In many parts of the body, such as the buccal cavity, the outbreak of cancer is commonly preceded by obvious hyperplastic changes (leucoplasia) in the surface epithelia. Moreover, it is noticeable that these lesions are seldom limited to the precise starting-point of the cancerous disease. This clearly implies that the abnormal activity, which at a given spot culminates in cancer, affects in a less degree the adjacent epithelia of the region for a considerable extent. Lesions of this type are commonly, but very erroneously, regarded as "inflammatory" in origin, that is to say, as the outcome of extrinsic causes; whereas, my belief is, that these morbid conditions are the result of proliferative hyperplasia of intrinsic origin, in which altered metabolism of the local cells plays the chief part. The question occurs whether all parts of the body, in which cancers arise, are not similarly circumstanced. The indications at present forthcoming are decidedly in favour of an affirmative answer; the admirable researches of Heidenhain[1] have, at any rate, answered the question in this sense for the female breast. He has conclusively shown that every mamma containing a cancerous tumour, is diseased throughout. Its secretory cells are unduly numerous, and they everywhere show signs of excessive proliferative activity; while, the peri-acinous connective tissue is much increased, its nuclei are unduly abundant, and it is infiltrated with small round cells. Parts in such a condition, are evidently more prone to originate cancer, than perfectly normal structures.

Changes of this kind indicate regional, as well as local structural proclivity.

**Local Dissemination.**

As previously mentioned, at a comparatively early stage of the disease, there may usually be found in the vicinity of the primary tumour, or even at some distance from it, small satellite nodules, which are the first obvious signs of local dissemination.

Careful histological examination of these nodules and their connexions by serial sections etc. shows that, as a rule, they are directly continuous with the parent tumour by means of cord-like processes of cancerous growth, which spread by way of the adjacent lymphatics and small veins. It is noticeable, as Seelig, Hoggan and other histological investigators of this matter have specially pointed out, that the endothelial cells of the intima take no part in the morbid process; and, for a considerable time, maintain their integrity, in spite of this invasion.

There are good reasons for believing that the local dissemination of cancer is chiefly effected in this way, that is to say, by the continuous

[1] *Arch. f. klin. Chir.*, 1889, Bd. xxxix., S. 97.

centrifugal extension of ingrowing cancerous processes, or by "permeation," as Handley calls it.

As I showed many years ago,[1] the disease often spreads in this manner to localities at a considerable distance from the primary tumour, *e.g.* in cancer of the breast, the mediastinal tissues, pleuræ and intra-thoracic organs may be thus invaded; and, in like manner, the disease may be conveyed from one breast to the other, to the upper end of the humerus, sternum etc.

Since each of these local dissemination nodules constitutes a fresh centre of the disease, which progresses like the parent tumour, it is obvious that cancer may be widely disseminated by "permeation."

Billroth seems to have had an inkling of this, for he long ago wrote, with regard to the dissemination of mammary cancer in the liver: "My idea is that the cancerous material is directly transported through the lymphatics of the mediastinum, diaphragm and suspensory ligament of the latter."[2]

There can be no doubt that this continuous centrifugal spread of the disease by direct extension, is greatly favoured by the many direct communications between the lymphatic and venous radicles to which Leaf[3] has lately called attention, for the venous route is as important for "permeation," as the lymphatic route.

While, however, conceding, as I always have, the paramount importance of this method for local dissemination, I am unable to support Handley[4] in his contention, that "permeation" is the alpha and omega of dissemination in general.

In addition to this method of direct extension, I think we must also recognize the fact, that cancer is often spread by the conveyance of cancer cells—detached from the primary tumour or its satellite offshoots—by the lymph and blood streams. Thus those really discontinuous, satellite nodules arise, which may constantly be found in the persons of those suffering from disseminated cancer.

In effecting detachment from the parent tumour, and in the subsequent course of their migration, especially in its early stages, dissemination is greatly aided by the spontaneous movements of the cancer cells, of which I have previously made mention.

This subject can be more satisfactorily investigated in the uterus, than in the mamma and most other organs; gynæcological pathologists (Hofmeier, Winter, Seelig and others) have reported and carefully studied, many striking examples of the discontinuous dissemination of cancer in this organ. Thus, in a considerable number of instances, primary cancer of the cervix uteri has been found concomitant with secondary cancerous foci of the same structure in the corpus, without there being any morbid alteration of the intervening parts; and, in a few cases, with the primary cancer in the corpus, secondary nodules have

[1] "Diseases of the Breast," 1894, chap. ix.

[2] In like manner Astley Cooper, whose knowledge of the anatomy and pathology of the breast was far in advance of his time, wrote: "The internal thoracic absorbents carry the diseased matter to the liver, which becomes tuberculated, and assumes the true scirrhous character" ("Lectures on Surgery," 1839, p. 376).

[3] *Lancet*, 1900, vol. i., p. 607. [4] *Ibid.*, 1905, vol. i., pp. 909, 983, and 1047.

been found in the cervix or portio. In all these cases, the most careful histological examination failed to reveal any direct continuity, between the primary and secondary tumours. Referring to such cases, Seelig says that the communication between the lymphatics of the cervix and corpus, is very much freer through the numerous large branches within the musculature, than it is through the much smaller branches uniting the mucosa of the two uterine segments; and he finds that in such cases as those we are now discussing, the disease disseminates along these lines.

Many similar instances have been reported in the mamma, and other parts of the body.

I shall subsequently have to refer to the facts relating to intra-vascular cancers, cancer emboli, and the presence of free cancer cells in the blood, which support this contention; as also to some other facts of similar import, concerning dissemination in lymph-glands and in distant parts.

The local dissemination of cancer, varies much in different parts, in respect to date of onset, direction, and extent; and, in the epithelial type of the disease, this form of dissemination is of more frequent occurrence, than in the connective-tissue type.

Thus, there is great difference as regards proclivity to local dissemination, between cancer of the breast, uterus, tongue, and "rodent" cancer of the skin; between periosteal sarcoma of the bones, the myeloid form of sarcoma, glioma etc.

Local dissemination has an important bearing, when the question of operation is under consideration; for, it appears from the following considerations, that the spread of the disease to the lymphatic glands and to the system generally, is greatly favoured by local dissemination. Thus, of 192 cases with local dissemination, Török and Wittelshöfer found the lymphatic glands invaded in 52·6 per cent., and metastases in 72·9 per cent.; whereas, of 174 cases free from local dissemination, the lymphatic glands were affected only in 42·5 per cent., and there were metastases in but 45·4 per cent.

### Lymph-Gland Dissemination.

One of the earliest consequences of the development of a cancerous tumour is, that the adjacent lymph-glands become enlarged. This condition may be only transitory, as in the glandular enlargements occasionally seen in the course of most infectious diseases, in association with certain non-malignant tumours, and in the glands left behind after extirpation of a cancerous part. Such enlargements are usually ascribed to "irritation," or "chronic inflammation."

Histological examination reveals nothing more than undue increase in number and size of the lymphoid cells, together with thickening of the fibrous reticulum, and proliferation of its nuclei, as well as hyperplasia of the endothelia. These changes cause obstruction of the lymph-sinuses; and consequent clogging of the circulation through the gland.

When associated with cancer, this glandular enlargement is usually followed, after a time, by the development in the affected glands of cancerous growths, similar in character and structure to the primary neoplasm. This indicates that the secondary growths are derivatives of the primary one. Yet it is exceptional to find any direct continuity between the two. Wherein, then, does the connexion consist? As I have previously mentioned, the cellular elements of malignant epithelial tumours, like their corresponding physiological prototypes, are very closely related to the lymph radicles. Hence detached cellular elements from the tumour, readily enter the lymphatics, where they have been seen and studied by Langhans, Waldeyer, Leopold, Seelig and others. No doubt this disconnexion of the cancerous cell from its normal nexus, and its transportation into the lymph-radicles, is effected largely by its own contractile and motor properties; which, as Klebs, Waldeyer and others have shown, are considerable—especially in its young state. The migration of leucocytes from the bloodvessels into the lymphatics, is a similar phenomenon, which has been demonstrated by Thoma in all its stages (1873).

But these considerations must not blind us to the fact that, even in the absence of any such active participation, cancer cells may nevertheless be transported into the lymphatics and carried by them into the adjacent lymph-glands, just as happens with the granular matter introduced in tattooing, with anthracite particles absorbed from the lungs of colliers and deposited in the bronchial glands etc. In the dissemination of cancer, besides the living cancer cells, no doubt many moribund, disintegrating cellular elements, and much granular *detritus* therefrom, as well as epiphytic microbes, are constantly being carried in one or other of these ways into the lymphatic glands. From the smallness of the lymph-radicles, it may be inferred that such transported fragments must be exceedingly minute—probably a single cell or a small cellular group in most cases. That epithelial cells thus dissevered from their normal connexions may still grow and multiply, we know from the familiar process of skin-grafting; and from Loeb's experiments in cultivating detached epithelial cells in blood-serum etc.

Probably all cancer cells are capable of dissemination; but all are not capable of growing when disseminated. There are good grounds for believing, that the majority of these "cancer emboli" perish and are absorbed, owing to the metabolic activity (phagocytosis) of the cells of the glands; and that only those with sufficient vitality to overcome this resistance originate dissemination tumours. Hence the lymph-glands form a temporary barrier to the spread of the disease; and do not themselves usually become affected until a considerable time after its primary outbreak.

Gussenbauer's [1] histological researches confirm this. He found traces of cancer cells disseminated in the glands of the neck, secondary to primary disease of the lip, in twenty-nine out of thirty-two consecutive cases, and doubtful evidence of it in the other three. Yet clinical experience proves, that when the primary disease is extirpated without removal of the adjacent glands, in a considerable proportion of cases, the latter

[1] *Zeitschrift f. Heilk.*, 1881, Bd. ii., S. 17.

do not originate recurrences. Similarly of Küster's[1] 117 breast-cancer extirpations, in which the excised axillary glands were microscopically examined, in only two instances were they found perfectly free from any signs of cancerous dissemination; and, of six cases of the same disease, with no enlargement of the axillary glands clinically appreciable, Gussenbauer nevertheless found—on histological examination after removal—evidence of dissemination in these glands in every case. But we know from clinical experience that, after extirpation of cancerous breasts without opening the axilla, recurrences in the axillary glands are proportionately much less frequent than this; thus of thirteen mammary cancers, with no appreciable enlargement of the axillary glands, for which the breast alone was removed, Hildebrand found that in three, there was no return of the disease three years and upwards after the operation.

We have thus arrived at the important conclusion, that the outbreak of the disease in the lymphatic glands is due to cells detached from the primary neoplasm, arrested there, which subsequently develop in accordance with their inherent tendencies. This explains the great resemblance always noticeable between the primary and secondary growths, the significance of which it is impossible to ignore. Moxon has sagely insisted upon this. He says: "The first cancer which appears has a likeness to the part in which it appears, and the secondary cancers arising from it have the likeness of that first cancer; and those who doubt that they came from that first cancer must show us why they have that likeness."

In this connexion, Waring's experiments are of interest; for they show that the cellular elements of the secondary, as well as of the primary growths, in cancer of the pancreas and stomach, produce the same ferments etc. as the normal secretory cells of these parts.

In the course of these researches it has been clearly established, that living cancer cells entering the lymphatics and lymph-glands, as a rule cause no coagulation of the lymph and no inflammation; when therefore occurrences of this kind result, it must be due to septic material brought by the cancer cells from their original *habitat*, as not infrequently happens. Similar conditions prevail when the lymphatics are invaded by continuous centrifugal extension; there is no coagulation or inflammation, unless the invading cancer cells are contaminated with septic material.

On examination of affected glands removed at an early stage of the disease, it can generally be made out that the new growth consists of but a few small, circumscribed foci, situated in the peri-follicular lymph-sinuses of the cortex, or in their immediate vicinity, that is to say, in the course of the normal afferent lymph-stream.

In a case of melanotic cancer of the breast with secondary lesions of the axillary glands, the dark colour of the cells enabled Billroth[2] to follow the extension of the dissemination along the lymph-sinuses; and his observations have since been confirmed and amplified by Zehnder.[3]

[1] *Verhand. der deutsche Gesellschaft. f. Chir.*, Bd. xii., S. 288.
[2] *Arch. f. path. Anat.*, Bd. xxi., S. 441.
[3] "Ueber Krebsentwicklung in Lymphdrüsen" (*Arch. f. path. Anat.*, 1890, Bd. cxix., S. 261).

The latter describes the initial foci as increasing in size by continuous proliferation of their constituent cells, which soon assume the alveolar arrangement, just as in the development of the primary tumour in the breast. These cells are very rich in karyokinetic figures; and they can easily be distinguished from the cells (lymphoid) of the parenchyma of the gland, which show no signs of proliferative activity, and appear not to participate in the spread of the disease. Petrick [1] has arrived at similar conclusions. Finally, by multiple staining, Gibbes [2] has conclusively demonstrated the correctness of this interpretation. Large multi-nucleated cells, the so-called "giant cells of cancer," are also of frequent occurrence. As the cancerous grafts increase in size, the parenchymatous cells of the gland suffer atrophy; the bloodvessels of the stroma enlarge, and their endothelial and muscular coats thicken. The endothelial cells of the lymph vessels and glands show no visible alterations, and they evidently take no active part in the process. In its subsequent course the disease progresses precisely as the primary outbreak.

Although the lymphatics connecting a cancerous tumour with the affected glands are usually free from disease, yet it occasionally happens, that they are found distended with cancer cells. The so-called lymph-cord, often to be felt passing from a mammary cancer to the axilla, is usually nothing but the pedicle of the axillary tail of the mamma itself. The glands first affected are usually those, that receive their lymph directly from the part of the organ involved by the primary neoplasm, and the subsequent spread of the disease from gland to gland, corresponds to the course of the lymph-stream; but, it must be borne in mind, that each affected gland constitutes a new centre of dissemination, and that the disseminative process may even progress against retrograde lymph currents and valves, as is the case when lymphatics are injected by anatomists.

In epithelial cancer we seldom meet with any general infection of the lymphatic system, such as is often observed in tubercle, syphilis, and other infective diseases. This important fact, taken with the foregoing considerations, is an indication against the resemblance traced by some pathologists, between these diseases and cancer.

The comparative frequency of lymph-gland dissemination and the period at which it is most prone to supervene, vary with the type of malignant disease, with locality, and even with different varieties of the same type of cancer in the same locality. These diversities depend chiefly upon the interactions of the following variable factors:—

(1) The size and quality of the cancer cells, and their degree of cohesion; (2) the comparative abundance or otherwise of the lymphatics in their vicinity, and the disposition of their radicles in regard to the cancer elements.

It is owing to the phagocytic properties of the invaded lymph-glands that early dissemination is not universal; and that a temporary barrier is offered to the spread of the disease.

[1] *Deutsche Zeits. f. Chir.*, Bd. xxxii., S. 530.
[2] *International Journal of the Medical Sciences*, August, 1889, p. 145.

I think there can be no doubt that the cellular elements of the epithelial tissues are more intimately connected with the lymph-radicles, under anatomical as well as under cancer conditions, than are the cellular elements of the connective tissue, under similar circumstances. Current conceptions as to the relation of the connective tissue with the lymphatic radicles, are mainly based on the histological researches of Recklinghausen with nitrate of silver staining (1862). According to these observations, the lymphatic radicles communicate freely with the connective-tissue interspaces, by means of numerous small canals (*saft-kanälchen*); and the walls of the lymphatics are perforated by small pores (stigmata). These interpretations of the histological appearances have always been objected to by those anatomists, who have studied the lymphatics by injection experiments, as the material employed was always found to be retained in the vessels. Recent researches of Ranvier [1] and others, are to the same effect; for they have shown that the lymphatics and lymph-radicles are quite shut off from direct communication with the surrounding connective tissue. This is probably the chief reason why local and lymph-gland dissemination is of more frequent occurrence with malignant epithelial, than it is with malignant connective-tissue tumours.

Gross' [2] analysis of a very large number of cases of both kinds of malignant tumour of the *mamma*, well illustrates this diversity, as follows :—

| | *Epithelioma.* | *Sarcoma.* |
|---|---|---|
| | Per Cent. | Per Cent. |
| Invasion of the skin .. .. .. | 68·92 | 9·67 |
| Invasion of chest wall .. .. .. | 21·58 | 3·87 |
| Invasion of para-mammary tissues .. | 8·39 | 0·64 |
| Lymph-gland dissemination .. .. | 67·35 | 0·64 |

It is probable, however, that the comparative frequency of lymph-gland dissemination in mammary sarcoma, is much greater than is indicated by Gross' analysis of promiscuously recorded cases; for, of 24 consecutive cases under my observation,[3] the axillary glands were affected in 2; of Poulsen's [4] series of 33 cases this condition was found in 15 per cent.; and of 45 similar cases by Campiche and Lazarus-Barlow,[5] the axillary glands were invaded in 7.

Ehrhardt [6] reports dissemination in the adjacent lymph-glands, in 49 of 131 patients with malignant epithelial tumours of the thyroid; and in 18 of 107 patients with sarcoma of the same part.

Of 10 malignant epithelial tumours of the prostate examined post-mortem, J. W. T. Walker [7] found that infiltrated lymph-glands were present in association therewith, in 6 cases.

Of 118 cases of primary epithelial cancers of the breast consecutively under my observation, there was obvious lymph-gland dissemination—when the patients were first seen—in 86, or in 73 per cent.; and of 44

[1] *Arch. d'Anat. microscopique*, Paris, 1897, t. i., p. 137.
[2] *American Journal of the Medical Sciences*, July, 1887, p. 17.
[3] "Diseases of the Breast," 1894, p. 438.
[4] *Arch. f. klin. Chir.*, Bd. lxiii., S. 592.
[5] *Archives of the Middlesex Hospital*, 1905, vol. v., p. 112.
[6] *Bruns' Beitr. z. klin. Chir.*, 1902, Bd. xxxv., S. 343.
[7] *Archives of the Middlesex Hospital*, 1905, vol. v., p. 157.

consecutive necropsies on those who had died of this malady, there was lymph-gland dissemination in 40, or in 90·9 per cent.

From this it follows, that dissemination in the adjacent axillary glands is, sooner or later, an almost invariable concomitant of acinous (scirrhous) cancer of the female breast ; the cases that run their entire course without it are of great rarity.

Of 68 cases of primary epithelial cancer of the mamma in males, tabulated by me, the axillary glands were obviously enlarged in 43, or in 63 per cent.

In the corresponding type of cancer of the cervix uteri, this form of dissemination is certainly of less frequent occurrence.

Thus, although a considerable number of uterine cancers run their entire course, without causing any obvious dissemination in the adjacent glands, yet it would be a mistake to suppose that lymph-gland dissemination is rare in uterine cancer ; for, as a matter of fact, the adjacent glands are invaded in the great majority of post-mortem cases. Thus, of my 78 necropsies, lesions of this kind were noted in 56, or in nearly 72 per cent. In 28 per cent., however, there was no obvious macroscopical glandular affection.

In cancer of the corpus uteri, local and lymph-gland dissemination is of slower and less frequent occurrence, than when the cervix is the part affected ; thus, an analysis of 33 necropsies for this form of cancer by Andriezen and Leitch, showed dissemination in the adjacent lymph-glands in only 15 cases, or in 45 per cent.

Malignant epithelial tumours of the tongue and mouth, disseminate in the adjacent lymph-glands even more frequently than cancers of the breast ; thus, of 104 cases consecutively under my observation, there was obvious lymph-gland dissemination—when the patients were first seen—in 86, or in nearly 83 per cent. ; and 57 post-mortem examinations revealed lymph-gland dissemination in 56, or in 98·2 per cent.

In epithelioma of the lower lip, this form of dissemination is much rarer, and of later advent, for of 72 primary cases examined by me, when first applying for surgical advice, only 36, or 50 per cent., presented obvious enlargement of the adjacent lymph-glands ; and, of 13 post-mortem examinations, 12 revealed lymph-gland dissemination, or 92·3 per cent.

Of 19 cases of primary epidermoidal cancer of the skin, the adjacent lymph-glands were invaded—when the patients were first seen—in 10, or in 52·6 per cent. ; and of 5 necropsies, on those who had died of this disease, in all the adjacent lymph-glands were cancerous.

In 28 cases of "rodent ulcer," I found that the adjacent lymph-glands were invaded by the disease in 4, or in 14·3 per cent. (in all of these instances the disease was recurrent) ; and, of 4 necropsies on those who had died of this malady, none presented lymph-gland dissemination.

In cancer of the stomach the adjacent lymph-glands are very often invaded. This was the case in 89·6 per cent. of N. Moore's[1] 29 necropsies ; in 87 per cent. of the cases specially examined *ad hoc* by Cunéo ;[2] and in

[1] *Lancet*, 1889, vol. ii., p. 418.

[2] "De l'envahissement du système lymphatique dans le cancer de l'estomac," Paris, 1900.

70·4 per cent. of H. Colwell's[1] 115 necropsies. Besides this, local dissemination in the liver, and adjacent parts was of frequent occurrence.

Renner's[2] special study of 15 gastric-cancer cases gives similar results. He very seldom found the regional lymph-glands uninvaded. The usual mode of extension was by the lymph-channels: the subpyloric glands were invaded in 60 per cent. of the cases, the supra-pancreatic in 49, those of the small curvature in 45, the retro-pyloric glands in 42, those of the cardia in 26 per cent.; and the sacral, lumbar, and mediastinal glands in 58 per cent., the bronchial glands in 41, and the mesenteric in 22 per cent.

In that curious form of malignant disease known as *chorio-epithelioma* or *deciduoma malignum*, the precise status of which has yet to be determined, it is noticeable that—so far as its disseminative features are concerned—it presents far more resemblance to sarcoma than to epithelioma; thus, notwithstanding the very great frequency of general dissemination in this malady, lymph-gland invasion is very rare, Teacher[3] having found only eight instances of this kind in the numerous cases tabulated, or about 4 per cent.

These illustrations suffice to show the differences with regard to lymph-gland dissemination, between the varieties of the epithelial type of cancer; and similar diversities are also met with among the various forms of sarcoma, of which the following examples will suffice.

Of 17 consecutive cases of primary sarcoma of the upper jaw under my observation, the adjacent lymph-glands were obviously enlarged, when the patients first applied for surgical advice, in 7 cases, or in 41·2 per cent.; and, of 8 fatal cases submitted to post-mortem examination, in 4 the adjacent lymph-glands were invaded.

Sarcomata of the long bones—the most malignant of tumours—seldom disseminate in the lymph-glands, although general dissemination occurs in nearly one-half of the total cases; thus, of Gross'[4] 165 cases, lymph-gland dissemination was met with only in 3·7 per cent.; but, of these cases, 70 were myeloid tumours, which very rarely spread to the lymph-glands.

Of 36 sarcomata of the long bones,[5] many of which were under my observation, adjacent lymph-glands were invaded in 7, or in 19·4 per cent., only 3 of these tumours being of the myeloid kind.

Of 35 sarcomata of the femur and tibia[6] tabulated by Butlin and Colby,[7] lymph-gland dissemination was met with in 5, or in 14·3 per cent.

As Gross has shown, the relative frequency of lymph-gland dissemination in sarcoma of the long bones, is chiefly dependent on the histological structure of the tumour; thus, he found that the spindle-celled and myeloid forms of the disease hardly ever caused lymph-gland dissemina-

[1] *Archives of the Middlesex Hospital*, 1906, vol. vii., p. 151.
[2] *Mitth. a. d. Grenzgeb. d. Med. u. Chir.*, Bd. xxii., Heft 2, S. 131.
[3] *British Journal of Obstetrics and Gynæcology*, August, 1903, p. 145.
[4] *American Journal of the Medical Sciences*, July, 1879. The initial seats were femur in 67, tibia 47, humerus 21, fibula 13, ulna 7, radius 6, radius and ulna in 1 case.
[5] Femur 17, tibia 6, humerus 8, fibula 3, and radius 2.
[6] Femur 22, tibia 13.
[7] St. Bartholomew's Hospital Reports, 1895, vol. xxvi.

tion, while with round-celled forms the adjacent lymph-glands were invaded in from 6·25 to 8·33 per cent. of all cases.

Melanotic malignant tumours of the skin, which have hitherto generally been regarded as predominantly sarcomatous, behave with regard to lymph-gland dissemination more like epithelioma; for, of 115 cases by Ebermann, Eiselt, Coley and Pemberton, I find that 48, or 41·7 per cent., disseminated in the adjacent lymph-glands.

Sarcomata of the uveal tract, nearly all of which are choroidal—221 of 259 according to Fuchs—hardly ever invade the adjacent lymph-glands, although general dissemination is frequent.

With retinal gliomata, lymph-gland dissemination occasionally occurs, while general dissemination is rare.

It is stated of malignant tumours of the tonsil and testis, whether epitheliomatous or sarcomatous, that they disseminate with great frequency in adjacent lymph-glands.

Thus, of 10 cases of primary malignant disease of the tonsil, most of which were under my observation, 6 were of epithelial and 4 of connective-tissue origin; of the former group, the adjacent lymph-glands were invaded in every case; and of the latter group, in every case save one.

Of 12 cases of malignant disease of the tonsil tabulated by Butlin,[1] 9 were of connective-tissue and 3 of epithelial origin; and in all, save one sarcoma case, the adjacent lymph-glands were invaded.

With regard to malignant disease of the testis, of 20 cases of epithelioma collected by Butlin,[2] lymph-gland dissemination was found in every case fully examined; and, of 14 cases of sarcoma similarly examined, only 3 were exempt from this form of dissemination.

In the ovary, malignant epithelial tumours usually disseminate in the adjacent lymph-glands, and this was the condition in 5 of 9 cases under my observation; but sarcomatous tumours of this part invade the lymph-glands less frequently.

It may be inferred from these illustrative details that sarcomata, as compared with epitheliomata, rarely disseminate in the adjacent lymph-glands; but there seem to be some exceptions to this rule, especially in the tonsil and testis, whence it may be inferred that, in these localities, the lymph-radicles attain more intimate association with the tumour elements, than is usual elsewhere.

It is also noticeable, that the small round-celled and lymphoid varieties of sarcoma are more prone to invade the adjacent lymph-glands, than other forms of sarcoma.

The number of lymph-glands in a given locality, commonly affected by cancerous dissemination, often greatly exceeds the number of such glands discriminated by anatomists under normal conditions; for instance, about a dozen lymph-glands are normally to be found in the axilla in the course of ordinary dissection, but, in cases of mammary cancer, the number obviously noticeable is much greater. Thus, in a mammary-cancer patient operated on by Gross, fifty diseased glands were removed, which varied in size from a small shot to a large nut. I have seen several instances, in which the number was nearly as great. This condition is

[1] "Sarcoma and Carcinoma," 1882. [2] *Op. cit.*

no doubt due to morbid enlargement of the numerous, small, lymph-glandular structures normally present in the axillary fat, although ordinarily invisible to the naked eye.

The number of glands usually affected is of course much less than this, but half a dozen or more are often obviously diseased; yet the resulting tumours seldom attain large size. When, however, only a few glands are involved, or but a single one, tumours larger than usual often ensue. Cancerous glands generally remain discrete; but sometimes they blend together, forming a single hard, irregular, nodular mass.

It is a matter of considerable practical importance to determine, how soon after detection of the primary neoplasm, the lymph-glands become diseased. According to Fink,[1] in mammary cancer, this happens as early as from the sixth to the twelfth month; and, after the thirteenth month, the glands are invariably invaded. Winiwarter estimated the period at from 14 to 18 months. Gross gives the average as 14·7 months. These are but clinical data, which, of course, do not enable us to affirm that the glands are free from disease for the whole period of apparent immunity.

In 43 of Küster's cases, with no clinically appreciable disease of the glands, signs of cancerous dissemination were, nevertheless, found in them, on histological examination after removal. On the other hand, Poulsen reports 21 cases in which the mamma was removed for cancer—the axilla not being touched—in which the patients afterwards remained free from recurrence for three years, or more; although, in several of them, the disease had existed for long periods prior to operation.[2] Schmidt and others have met with similar cases; hence there are evidently exceptions to the rule of early, effective, lymph-gland dissemination.

Similar indications have been met with in cancer of the cervix uteri. As evidence of the comparative rarity of dissemination in the adjacent lymph-glands, in the early stage of this disease, reference may be made to the fact, that in extirpating cancerous uteri surgeons have seldom met with obviously infiltrated glands; moreover, after extirpation, glandular recurrence is decidedly rare.

According to Winter,[3] lymph-gland dissemination is present in from 20 to 30 per cent. of all uterine-cancer patients seeking surgical relief; but Peiser [4] estimates the proportion at 50 per cent.; while Schauta,[5] found lymph-gland dissemination in 57·6 per cent. of his 60 post-mortem cases, in most of which the disease had run its natural course.

Recent experience of surgeons with the radical operation for the complete removal of the cancerous uterus by laparotomy, has caused renewed attention to be paid to this subject; thus, in a series of 76

[1] *Zeits. f. Heilkunde*, 1888, Bd. ix., S. 453.

[2] In one of Poulsen's cases the disease had existed for seven years before operation, in which only the breast was removed, the axilla not being opened; she was well and free from recurrence, when last seen, several years afterwards. Five other similar cases, in which the disease had lasted for several years before removal of the breast, without opening the axilla, were also free from recurrence years afterwards.

[3] *Zeitschr. f. Geb. u. Gyn.*, 1893, Bd. xxvii., S. 101.

[4] *Ibid.*, 1899, Bd. xxxix., Heft 2.

[5] *Monatschr. f. Geb. u. Gyn.*, 1904, Bd. xix., Heft 4.

operated cases of early cancer of the cervix uteri, specially examined *ad hoc*, Wertheim [1] found—on histological examination—evidence of cancer in 22, or in 28·9 per cent.; of a number of similar cases tabulated by Wakefield,[2] there was lymph-gland dissemination in 25 per cent.

Yet, in spite of this ratio of involvement of glands in the early stage of the disease, a considerable proportion of patients are found to be free from any recurrence, five years and upwards after extirpation of the uterus by vaginal hysterectomy, in which operation the lymph-glands are not removed; thus, of 100 operations of this kind, T. Wilson [3] found that 33 per cent. of his patients were well and free from recurrence, five years and upwards afterwards, and Glockner's percentage of similar successful results was 35·6 per cent.

There are then good reasons for believing, that the majority of these "cancer emboli" perish and are absorbed, owing to the phagocytic activity of the lymphocytes of the glands; and that only those with sufficient vitality to overcome this resistance, originate dissemination tumours. Thus, the lymph-glands form a temporary barrier to the spread of the disease, and do not themselves usually become cancerous, until a considerable time after the primary outbreak.

In some very rare instances, glandular implication is so rapid, that it appears to coincide with or even to antedate the primary disease. In others, it may be delayed for several years—for ten years, or even more—or it may never occur at all. Certain cancers may undoubtedly run their entire course, causing systemic dissemination and death, without the adjacent lymph-glands ever being implicated. Hence, the absence of lymph-gland disease, is no absolute guarantee against general systemic dissemination; which in these cases evidently takes place through the bloodvessels. According to my experience, such occurrences are most exceptional in unoperated cases. I have met with but a single instance of this kind, in 44 consecutive necropsies on patients who had died from mammary cancer, there being metastases in 28.

According to Gross, metastases occur without any antecedent lymph-gland dissemination, in about 1 in 7 of all cases of mammary cancer.

This estimate appears to me too high, probably because many operation cases have been included. Török and Wittelshöfer's figures, which are much higher still, err also from this cause.

In 3 of the 4 cases in my list, free from lymph-gland disease, cancerous axillary glands had just previously been removed by operation.

Should anyone oppose to this conclusion Török and Wittelshöfer's analysis of 366 necropsies, in which the axillary glands were found invaded only in 175, or 48 per cent.; my answer is, that these statistics are useless for determining the point under consideration, because of the large number of operation cases they include, in which the affected lymph-glands had recently been removed.

It is commonly stated that the progress of the disease is much slower,

[1] *Cent. f. Gyn.*, 1901, No. 2; *ibid.*, 1902, No. 9, etc.
[2] *American Journal of Obstetrics*, October, 1903.
[3] *British Journal of Obstetrics and Gynæcology*, 1902, vol. i.

and the total duration of life much longer, in cases where lymph-gland dissemination is long delayed, than in those where the glands are attacked at an early period of the disease. I am not aware of any statistical evidence that can be adduced in support of this belief; but my impression is that it is well founded.

It is, however, clearly shown by statistics, that obvious lymph-gland affection is an important factor in determining the results attained by operations for the removal of the disease.

Thus, according to Gross, of 136 cases of extirpation of the breast for cancer, in 93 obviously diseased glands were removed; the total duration of the life of these patients averaged 39·3 months each, and local recurrence ensued on the average in 1·9 months; whereas, in 43 cases free from gland dissemination, the average duration of life was 52·7 months, and the average period of recurrence was 8 months. The latter, therefore, lived 13·4 months longer than the former; and when recurrence followed, it appeared 6·1 months later.

Poulsen's testimony is to the same effect, for 22 per cent. of his operated cases (in most of which the glands were not obviously affected) were well for three years or more, after extirpation; whereas, of 43 operated cases (in which the glands were demonstrably involved), only 4 (9·3 per cent.) were well at the end of that period.

These data indicate that the best time for extirpating the disease is, before the glands have become obviously involved.

In a certain proportion of these cancerous glands, the disease is complicated by the supervention of inflammation and suppuration; owing, as Zahn [1] and others have shown, to their inoculation with pyogenic microbes, detached from the primary neoplasm, with the original "cancer emboli."

## Lymph-Gland Dissemination viâ the Thoracic Duct.

X In 1886 Troisier [2] published an essay, specially calling attention to the frequent association of intra-abdominal cancer—especially of the stomach—with enlargement of the left supra-clavicular lymph-glands; and insisting on the value of this indication, "*adênopathie externe à distance*," as a revealing symptom of intra-abdominal malignant disease.

Cases of this kind had previously been noted by Virchow, Leube, Henoch and others; but, until Troisier called special attention to the matter, neither clinicians nor pathologists seem to have recognized its importance.

In our country, this kind of knowledge has penetrated very slowly, notwithstanding frequent reminders from Troisier and others. The first example of it, recorded as such, was reported by myself in 1895;[3] yet even now—such is the lack of perspicacity—cases of this kind are generally regarded by British clinicians and pathologists as rare novelties.

[1] *Arch. f. path. Anat.*, etc., Bd. cxvii., S. 209.

[2] *Bull. et Mém. de la Soc. Méd. des Hôpitaux*, 1886, p. 394; also *ibid.*, January 13, 1888; and *Arch. Gén. de Méd.*, February and March, 1889, pp. 129 and 297; and *ibid.*, August, 1893, p. 423; also *C. R.* 13e *Cong. Internat. de Méd.*, Paris, 1900, t. iii., section d'anat. path., p. 42.

[3] *Lancet*, 1895, vol. ii., p. 262.

In the case referred to, the patient—a married woman aged fifty-six, the mother of six children, having for some months suffered from progressive anæmia and loss of strength, together with failure of appetite, constipation, nausea, and dyspeptic symptoms—in August, began also to experience pain in the epigastric region, for which she consulted a medical man in September.

I first saw her in the following October, when she was markedly anæmic and sallow. The ingestion of solid food caused epigastric pain and, after a time, nausea and vomiting. She complained of a swelling in the epigastric region; but, upon examination, no intra-abdominal tumour could be detected. There were no signs of obstruction. The liver and spleen seemed normal. There was no history of hæmatemesis or coffee-ground vomit. At this time, she was very subject to alternate flushing and pallor of the cheeks and extremities, the fingers often becoming quite dead, as in Raynaud's disease. She was also subject to palpitation of the heart, and to occasional syncopal attacks. The urine contained neither sugar nor albumen. Under the influence of rest in the recumbent position, with none but peptonized fluid foods, together with suitable medicine, the pain subsided and there was temporary improvement. It soon became obvious, however, that the weakness was increasing; and subsequently nausea, vomiting, and thirst became prominent symptoms. In the following January I saw her again, when she was weaker, paler, and more sallow than on the previous occasion. I was unable to detect any intra-abdominal tumour. The case presented many of the features of pernicious anæmia. She was treated with "bone-marrow" and Fowler's solution. This treatment soon had to be given up, on account of the pain and vomiting excited. In April, an intra-abdominal tumour was discovered.

I saw her again in May, when the emaciation, pallor, and weakness were very great. The vaso-motor symptoms had quite disappeared. Nausea, vomiting and epigastric pain, after food, still continued; but there was no hæmatemesis. On abdominal palpation, a circumscribed mobile, intra-abdominal tumour, about the size of a small turnip, could be felt rather to the right of the median line, midway between the umbilicus and xiphoid. It was dull on percussion. There appeared to be no dilatation of the stomach; the dimensions of the liver and spleen were normal; there was no umbilical retraction. The left supra-clavicular lymph-glands, as well as those at the upper part of the axilla, were enlarged and hard; these, by interfering with the venous circulation, had caused œdema of the face, head and forearm, this condition being of rather less than a week's duration. It was evidently due to dissemination of the disease in the glands at the root of the neck, through the medium of the thoracic duct. The recognition of this symptom, completely negatived any exploratory operation. Death ensued about five weeks later, and there was no necropsy. The patient was partially unconscious, with muttering delirium, for some days before the end. The rapid formation of the tumour, its mobility, the considerable size attained, the absence of hæmatemesis, gastric obstruction, hepatic and splenic enlargement, and finally the dissemination by the lymphatics, all seemed to indicate malignant intra-abdominal tumour—probably of omental origin.

In this condition, some of the superficial glands at a distance from the primary disease, become enlarged, without any of the intervening structures necessarily being invaded.

The glands usually thus affected are those of the left supra-clavicular region; but quite exceptionally the right supra-clavicular, inguinal, axillary, epitrochlear or other glands may be involved.

These may be affected conjointly with the supra-clavicular glands, or as isolated manifestations. Of 37 supra-clavicular adenopathies tabulated by Rousseau,[1] in 29 the glands of the left side were affected; in 4 those on the right, and in 4 those on both sides.

Although in the majority of these cases, the glandular enlargement turns out to be cancerous; yet this is not always the case, for I have witnessed retrocession, and so has Girode: in such cases we probably have to do merely with septic infection from a distant cancerous growth; and this type of adenopathy may cause painful sensations in the neck, shoulder and arm, which are otherwise generally absent.

But enlargement of the left supra-clavicular glands may also occasionally result, from such non-cancerous affections as gastric ulcer, tubercle of the lung, as well as from other tuberculous and even syphilitic lesions.

Moreover, this adenopathy must not be confounded with the "*pseudo-lipôme sus-claviculaire*" of Verneuil, of which I have elsewhere given an account,[2] which is simply an overgrowth of the fibro-fatty tissue of the supra-clavicular fossa—both sides usually being affected—those most liable being middle-aged women otherwise in good health.

At first, only a single gland is usually involved, then others of the group become affected, and these agglomerate. Pressure symptoms are comparatively rare, but I have seen an instance in which an affection of this kind caused œdema of the face and upper limb; and the lymph circulation through the thoracic duct may be blocked by the glandular tumour compressing it in the supra-clavicular vicinity, as in cases reported by Hillier, Menetrier and Glauckler.

This form of adenopathy is usually a late symptom; but, in some cases, it has been known to supervene a year or two before death.

It seems probable that this curious pathological condition is due to regurgitation of lymph—charged with cancer cells—from the thoracic duct, into the adjacent cervical glands; which lymph is presumably conveyed to the thoracic duct, by lymphatics derived from infiltrated lumbar glands.

It accords with this, that, in these cases, cancer cells and cancer thrombi have often been found free in the thoracic duct, without the circulation through it being arrested; and this is the usual condition. In other cases, the duct is partially or completely occluded by the growth of cancer within it; and thus it may be reduced to the condition of a

[1] "De l'adénopathie sus-claviculare," *Thèse de Paris*, 1895.
[2] Transactions of the Pathological Society, London, 1890, vol. xli., p. 302.

solid cord. Under these circumstances, chylous ascites may occasionally be met with. It is astonishing how freely cancer will grow within hollow, circumscribed structures, such as the thoracic duct, ureter, veins etc., when once it has gained entry, and this without necessarily implicating the encompassing wall; thus, I have seen a case in which a process of cancerous growth from the uterus, having perforated the lower end of the ureter, grew upwards in it to the pelvis of the kidney, without having invaded its walls, so that the long cancerous process could be removed entire from within the ureter, when the latter was laid open.

Supra-clavicular adenopathy is fairly often met with in the absence of visceral dissemination; but, of course, it generally implies antecedent invasion of the lumbar or other lymph-glands discharging into the thoracic duct, although in a few instances nothing of the kind has been noticed post-mortem.

I need hardly insist on the importance of this adenopathy, as a contra-indication to operation; and as an element in the diagnosis of obscure intra-abdominal disease.

In nearly half of the recorded cases, the seat of the primary malignant affection has been in the stomach: instances of this kind have been reported by Troisier,[1] Vidal,[2] Rousseau,[3] Belin,[4] Babes,[5] Stevens,[6] Spinelli,[7] Hillier,[8] Menetrier and Glauckler,[9] Schramm [10] etc.

Next to the stomach, most cases have been met with in association with uterine cancer; examples of this kind have been noted by Troisier, Spinelli, Rousseau, Faidherbe, Petit,[11] Kirmisson,[12] Hillier,[13] Unger,[14] Raymond [15] etc.

Secondary to cancer of the pancreas, Troisier's symptom has been seen by Nathan Raw [16] and Schramm.

Troisier and Poncet [17] have noted its concomitancy with cancer of the testis; Hurlemont [18] with cancer of the prostate; Hillier with sarcoma of the ischio-rectal fossa; Troisier with malignant disease of the adrenal etc.

Viannay [19] has directed attention to the value of inguinal adenopathy, as a revealing symptom of many pelvic and abdominal forms of malignant disease. In more than a quarter of all cases of uterine cancer, I found that the inguinal glands, of one or both sides, were obviously enlarged: in cancer of the cervix this is generally a late sign, but when the disease

1 *Op. cit.* 2 *Bull. et Mém. de la Soc. Méd. des Hôpitaux*, December, 1893.
3 *Op. cit.* 4 "Des adénopathies externes à distance," *Thèse de Paris*, 1888.
5 *Ann. de l'Hist. Path. de Bucharest*, 1894-1895, t. vi., p. 405.
6 *British Medical Journal*, 1905, vol. i., p. 929.
7 *Rivista di Clinica e Terapia*, 1893, No. 8, p. 397.
8 *Archives of Middlesex Hospital*, 1904, vol. iii., p. 117.
9 *Bull. et Mém. de la Soc. Méd. des Hôpitaux*, 1902.
10 *Berlin. klin. Woch.*, October 26, 1896.
11 *Bull. et Mém. de la Soc. Méd. des Hôpitaux*, 1888, t. v., p. 26.
12 *C. R. Soc. Anat. de Paris*, 1875, l., p. 571.
13 *Op. cit.* 14 *Arch. f. path. Anat.*, 1896, Bd. cxlv., S. 58.
15 *Bull. et. Mém. de la Soc. Méd. des Hôpitaux*, 1886, t. iii., p. 441.
16 *British Medical Journal*, 1905, vol. i., p. 1380.
17 *Lyon Méd.*, December 31, 1893.
18 "De l'adenite sus-clav. cancéreuse dans le carcinôme de la prostate," *Thèse de Lille*, 1896. 19 *Lyon Méd.*, September 22, 1901.

starts at or near the fundus, these glands may become affected at a comparatively early stage of the disease. Viannay found inguinal adenopathy noted, in 25 of 60 collected cases of cancer of the prostate; and in 9 of 62 cases of cancer of the bladder. I found the inguinal glands enlarged in 12 of 42 cases of cancer of the rectum.

Inguinal adenopathy has also been noted in association with cancer of the vagina, anus, ovary, stomach, large and small intestine, liver, pancreas, and even sometimes with cancer of the œsophagus and other intra-thoracic organs.

Whippham [1] has described an example of cancer of the appendix cæci, with supra-clavicular and inguinal adenopathy.

## General Dissemination.

The appearance of cancerous growths in various parts of the body, remote from the primary disease and its offsets—the so-called *metastasis* [2]—is one of the most striking features of malignant tumours, the commonest seats of these disseminative lesions being the liver, lung, osseous system, kidney, brain, pancreas etc. As mentioned in the opening chapter of this work, there is nothing specific of malignancy in dissemination *per se.*

Do benign tumours ever disseminate in this way; and can such dissemination originate from the constituent elements of parts free from any kind of tumour?

If we look only at the conclusions of those who have made special study of the remarkable series of events comprised under such headings as "deportation of chorionic villi," "deciduoma" benignum and malignum etc., we shall be constrained to answer both of these queries in the affirmative.

Of similar import is the occurrence of large cancerous tumours in lymph-glands and in internal organs, secondary to primary lesions so minute, unprogressive and unlike cancer, as hardly to be revealed even by skilled examination *ad hoc*, of which many striking examples have been reported,[3] and some I have myself seen.

Similar inference may be drawn from the many instances known to me, of malignant disease developing in the track of operation wounds, at various periods after the removal of non-malignant tumours, of which

[1] *Lancet*, February 2, 1901.

[2] The term "metastasis" was originally applied to these manifestations, under the belief that the disease really shifted from one part to another; and, as a matter of fact, some local diminution of the primary lesion commonly coincides with the outbreak of general dissemination. The term originated in general pathology, and was subsequently imported into tumour pathology; in the former, its use was suggested by such morbid manifestations as are often seen in mumps, when an outbreak of testicular inflammation not unfrequently follows the subsidence of the original parotid malady, etc.

[3] J. Hutchinson (*Archives of Surgery*, January, 1891, p. 220; and April, p. 349), cutaneous melanotic staining with dissemination; Butlin (*British Medical Journal*, 1892, vol. ii., p. 1343), epidermoidal cancer of the lymph-glands of the groin in a chimney-sweep, with no obvious primary cancer of the scrotum or elsewhere; Paget ("Lectures on Surgical Pathology," vol. ii., 1853, p. 447) has described a similar case. I have seen an analogous condition in the lymph-glands serving the lower lip, the latter part being cancer-free. For further reference to this subject, *vide* Chapter XXIII.

numerous examples have been recorded of late, after the removal of non-malignant cystic tumours of the ovary, uterine myomata etc.

It also seems to me that certain exceptional instances of the late recurrence of cancer, point in the same direction ; thus, in a case reported by Schmidt,[1] seven years after extirpation of a primary cancer of the breast, without local recurrence, the disease recurred in the liver ; and, I am indebted to the late Mr. Hulke, for the knowledge of a similar occurrence, more than ten years after extirpation of an eye for spindle-celled sarcoma of the choroid, without local recurrence.[2]

Here also mention may be made of the pseudo-plasms due to yeast infection, described by Busse and Curtis,[3] which disseminated in their human hosts ; and also caused disseminative tumours in the animals into which they were inoculated. The similar tumours caused in various animals by inoculation with certain pathogenic yeasts—as described by Sanfelice and his followers—many of which disseminated, also belong here. Moreover, many instances of dissemination in cases of mycosis fungoides, have also been reported.

In this connexion we must recollect the contagious venereal pseudo-plasms of dogs ; and the somewhat similar tumours of mice and rats, which have lately attracted so much attention as cancer prototypes,[4] all of which non-cancerous lesions are also apt to disseminate.

Such then are the indications, which seem to point to an affirmative answer to our queries.

On the other hand, there is the important fact that, in human pathology, non-malignant tumours and the elements of the normal physiological tissues, seem never to originate metastatic growths.

There are, however, some pathologists who challenge this apparently obvious proposition, alleging that certain non-malignant tumours, and physiological tissues, may indeed originate metastases. Thyroid adenomata, and the goitrous thyroid are specially implicated by these allegations ; while claims of this kind have also been advanced against ovarian cystic tumours, uterine myoma, hepatic adenoma, cystic adenoma of the testis, chondroma, osteoma, lipoma and angioma.

The controversy relating to this matter, concentres in the question of thyroid metastases : these occur with great frequency in malignant disease of the thyroid—in 85 per cent. of all post-mortem cases, according to Ehrhardt,[5] the lungs and the bones being their commonest seats.

According to Limacher, metastases are associated with malignant epithelial tumours of the thyroid in 92·1 per cent. of all cases ; and with sarcomata in 79·5 per cent.

[1] *Bruns' Beitr. z. klin. Chir.*, Bd. iv., Heft 1.

[2] The patient was an engineer, aged twenty-one, whose eye was extirpated by Mr. Hulke at the Royal London Ophthalmic Hospital on April 2, 1862, symptoms of the disease having existed for two years previously. In the autumn of 1872, this patient was seen by Sir W. Gull and Dr. Murchison for enlargement of the liver, there being then no sign of any recurrence in the orbit. He died some months later, when the liver—which weighed 20 pounds—was found to contain huge masses of spindle-celled sarcomatous growth.

[3] *Vide* Chapter X. [4] *Vide* Chapter VIII.

[5] *Bruns' Beitr. z. klin. Chir.*, 1902, Bd. xxxv., S. 343.

With the epithelial type of malignant disease, the lungs are invaded in 42 per cent., the bones in 29 per cent., and other parts in order of decreasing frequency as follows:—the kidney, pleura, brain, liver, omentum, adrenal, myocardium, pericardium, intestine, ovary, mamma, diaphragm and stomach.

With the sarcomata, the lungs are invaded in 48 per cent., the bones in 18 per cent., and the other parts as follows:—liver, kidney, pleura, brain, myocardium, intestine, adrenal, spleen, stomach and pancreas.

Of the bones affected, the following analysis of 75 cases, indicates the special proclivities:—skull 31, inferior maxilla 30, sternum 18, vertebra 16, rib 12, femur 11, humerus 10, pelvis 9, scapula 4, zygoma 3, clavicle 1 and palate 1.

Cohnheim [1] was the first who maintained that metastases arose from "simple goitre"; and, since the report of this case appeared, about a score of others—of similar import—have been published.

Recklinghausen [2] declined to accept Cohnheim's "simple goitre" as such, maintaining that it was a "jelly carcinoma," and Wolfler [3] was of the same opinion.

Since then, the various investigators have been much divided in opinion, as to the real character of the primary, as well as of the secondary, lesions.

Here it must be noted that the difficulty in discriminating between normal thyroid, goitrous thyroid, thyroid adenoma and thyroid cancer, is admitted by all experts to be very great: thus Hugnenin says: "But few features, upon which the distinction is usually based in differentiating benign and malignant tumours of other parts, can be relied on for differentiating between benign and malignant tumours of the thyroid." Berry [4] likewise writes: "Instances are not unknown of simple adenoma being described as carcinoma, while obviously malignant infiltrating tumours have been pronounced to be adenomas. Even those who have had large experience in the microscopic examination of thyroid tumours will admit, that it is often difficult to say where adenoma ends and carcinoma begins."

Another source of fallacy arises from the well-known fact that, in thyroid cancer, the initial lesion is often so small as to escape notice, even after careful macroscopic and microscopic examination of the part: thus Hugnenin, having had occasion to examine a case of reputed "colloid goitre" with dissemination in the dorsal vertebræ, found after prolonged research a minute primary cancerous tumour in the goitrous gland. In reference to this matter Hugnenin says: "All the hitherto published cases of struma and thyroid adenoma, with metastasis, I regard as being really cancerous."

It accords with this interpretation, that the localities invaded and the character of the lesions, in these secondary tumours of so-called non-malignant thyroids, are similar to those met with in undoubted cases of primary thyroid cancer. For a fuller account of cases of alleged

[1] *Arch. f. path. Anat.*, 1876, Bd. lxviii., S. 547. [2] *Ibid.*, Bd. lxx.
[3] *Arch. f. klin. Chir.*, 1883, Bd. xxiv., S. 754.
[4] "Diseases of the Thyroid Gland," 1901, p. 199.

non-malignant thyroid metastasis, reference may be made to the publications of Patel,[1] Hansel,[2] Coats,[3] H. Morris [4] and Haward.[5]

Similar objections hold against the occurrence of non-malignant metastasis in other parts of the body; and, in my book on "Uterine Tumours,"[6] I have specially indicated the fallaciousness of the facts adduced to this end, with regard to uterine myoma.

From a general review of the *ensemble* of the subject, I conclude that the evidence hitherto adduced for non-malignant metastasis is inconclusive; and that the few instances in which it is alleged to have occurred, are capable of being otherwise explained.

The precise period at which the onset of general dissemination is likely to supervene is variable; but it is usually of rather tardy development, in respect to the average duration of life of the particular variety of malignant disease under my consideration. Thus, with malignant epithelial tumours of the female breast—in which form of cancer the average duration of life, according to my calculation, is from four to five years[7]—metastasis may be expected to supervene some two or three years after the initial outbreak, and about fifteen months after invasion of the axillary lymph-glands. Winiwarter, Sprengel and Fink estimate its date of onset at twenty-five months, Henry at thirty, and Oldekop at thirty-eight months. As a rule, the slower the progress of the primary disease, the later metastases appear. Occasionally they form during the first few months; and at other times not until after the lapse of several years—even ten years or more.

According to Gross, of 100 metastases secondary to cancer of the female breast, 24 form within the first year, 3 in from thirteen to eighteen months, 18 in from nineteen to twenty-four months, 27 in from twenty-five to thirty-six months, and 28 after three years.

The average duration of life in this local variety of cancer, after the first appearance of metastasis, is about two years.

In the *ensemble* of their characters—histological and otherwise—metastatic cancers closely resemble the primary neoplasm; and when they differ it is generally *per defectum*. Thus, the hard and fibrifying primaries, comparatively often originate softer and more cellular secondaries; and, although black cancers generally cause black metastases, green cancers green metastases, and similarly with ossifying, calcifying, chondrifying and other varieties, yet, in the secondaries, these special features are sometimes deficient or they may be altogether lacking.

Very exceptionally, however, we see the converse of this; for, as Virchow has shown, some cancers—not obviously pigmented—may nevertheless give rise to metastases in which pigmentation is a marked feature.[8]

[1] *Rev. de Chir.*, 1904, t. xxxix., No. 3, p. 399.
[2] *Beitr. z. klin. Chir.*, 1899, Bd. xxiv., Heft i.
[3] Transactions of the Pathological Society, London, 1887, vol. xxxviii., p. 399.
[4] *Ibid.*, 1880, vol. xxxi., p. 259.
[5] *Ibid.*, 1882, vol. xxxiii., p. 291.
[6] *Vide* p. 88.
[7] "Diseases of the Breast," 1894, p. 365.
[8] R. L. Thompson has described an instance of choroidal sarcoma, partly pigmented and partly non-pigmented, which gave rise to metastases, some of which were pigmented, some non-pigmented, and others in which these two varieties were mixed.

Metastatic tumours also differ somewhat from their primaries in their relations to the surrounding tissues—in that they are generally more circumscribed, and less infiltrating in their mode of growth.

They also differ from the latter, in that they are usually multiple and spring up in several widely separated localities. Occasionally the number of metastases is very small; and in rare instances there may be only a single one, as in a case reported by Arnott,[1] in which epithelioma of the tongue disseminated in the left adrenal. In soft, vascular organs, like the liver, these growths often attain immense size; but in other parts they are commonly of moderate dimensions. Usually they present as small, hard, nodular, flattened or discoidal masses, which soon become cupped or umbilicated, owing to contraction of the older parts of the growth. Occasionally they take the form of diffuse infiltrations, especially in the pleura, peritoneum and bones.

In hollow structures such as the cavities of the heart, the large veins, the thoracic duct, and in the pleural and peritoneal sacs, free masses of metastatic cancer—generally embedded in more or less coagulum—have often been found.

Sometimes these growths are exceedingly numerous, and widely spread throughout the body, as in Velpeau's[2] remarkable case of mammary cancer, in which hundreds of them were found distributed throughout the general connective tissue, lungs, liver, bones, muscles, heart, stomach, duodenum, small intestines, pancreas, kidneys, gall-bladder, vena cava, peritoneum, dura mater and thyroid gland.

Similar cases have since been recorded by Bramwell[3] and Kautorowicz.[4]

I have seen it stated by good authorities, that metastases invariably affect both of paired organs; but I have convinced myself by repeated observations, that it is not so: both are usually affected, but often only one.

It is remarkable that the cancers of every locality have their own special modes of dissemination; and, even the different types and varieties of the disease, in particular organs, manifest diversities in this respect.

The sequence of the development of metastases and the combinations of organs invaded, are difficult to explain. The deep parts of the body are much more frequently invaded than the superficial; but, the order of eruption in most individual internal organs, is usually the converse of this.

In consequence of these peculiarities, before proceeding further with our study of dissemination, it is desirable to review briefly the incidence and relative frequency of metastases, as they are met with in the chief local manifestations of the epithelial and connective-tissue types of cancer.

[1] Transactions of the Pathological Society, London, vol. xix., p. 418.
[2] "Traité des Maladies du Sein," Paris, 1854.
[3] *Edinburgh Medical Journal*, July and August, 1894.
[4] *Cent. f. allg. Path.*, etc., 1893, No. 20.

## The Metastases of Malignant Epithelial Tumours.

As these lesions have been more fully studied in connexion with cancer of the female breast than elsewhere, I propose to begin the study of metastasis with this type.

The *female breast* is one of those parts in which the tendeney of dissemination is very great; thus, of 44 consecutive necropsies, many of which were made by myself, metastases were found in 28, or in 63·1 per cent.

This percentage would be considerably higher, but for the fact that 10 cases are included, which had terminated fatally shortly after extirpation of the local disease, and which were therefore presumably free from metastasis. Of the remaining 34 necropsies, in which death ensued in the natural course of the disease, there were metastases in 25, or in 73·5 per cent.

Of these 44 consecutive necropsies, the seats of metastases were as follows :—

| | | | |
|---|---|---|---|
| Liver .. .. .. | in 20 cases. | Mesenteric and omental glands .. .. | in 1 case. |
| Lungs (B. 5, L. 2, R. 1) .. | ,, 8 ,, | Gastro - hepatic omental glands .. .. .. | ,, 1 ,, |
| Pleura (B. 5, L. 1) .. | ,, 6 ,, | Peritoneum .. .. | ,, 1 ,, |
| Femur (B. 2, R. 1, L. 1) .. | ,, 4 ,, | Uterus .. .. .. | ,, 1 ,, |
| Retro-peritoneal glands .. | ,, 3 ,, | Ovary (L.) .. .. .. | ,, 1 ,, |
| Bronchial glands .. .. | ,, 2 ,, | Tibia (R.) .. .. .. | ,, 1 ,, |
| Humerus (R. 1, L. 1) .. | ,, 2 ,, | Ribs (B.) .. .. .. | ,, 1 ,, |
| Kidneys .. .. .. | ,, 2 ,, | Spleen .. .. .. | ,, 1 ,, |
| Supra-renals (B. 1, L. 1) .. | ,, 2 ,, | Duodenum .. .. .. | ,, 1 ,, |
| Pancreas .. .. .. | ,, 2 ,, | Mamma (of opposite side) | ,, 1 ,, |
| Vertebræ (lower dorsal and upper lumbar) .. | ,, 1 case. | | |

The *liver* is the organ most frequently affected with metastases in mammary cancer. My analysis shows this in a striking manner; but, it would have been otherwise, had I not carefully separated the true pulmonary metastases from those cases (twelve altogether), in which the lungs were invaded by direct extension of the primary disease or by its local dissemination. The discrepancy between my analysis, and those statistics which place the lungs and pleuræ at the head of the list, is evidently due to this cause.

Of 470 similar necropsies analysed by Campiche and Lazarus-Barlow,[1] metastases were found in 84·4 per cent.; while of Török and Wittelshöfer's[2] 366 necropsies, they were met with in 215, or in 58·7 per cent.

By massing the totals of these authors with Gross' cases, we get a total of 893 necropsies, with metastases having the following percentage distribution :—liver 46·8, pleura[3] 42·4, lungs[3] 42,3, bones[4] 26·5, lymph-glands[5] (exclusive of axillary and cervical) 19·0, mamma (of opposite side[6]) 12·9, kidney 7·2, pericardium 7, brain and meninges 6·6, ovary 6·5, peritoneum 6·2, stomach and intestines 4·9, supra-renal 4·6, spleen 3·7,

[1] *Archives of the Middlesex Hospital*, 1905, vol. v., p. 83.

[2] *Arch. f. klin. Chir.*, Bd. xxv., S. 873.

[3] I suspect many cases of direct lymphatic extension are comprised under these headings.

[4] The percentage site-incidence of these metastases were as follows: Cranium 24, vertebræ 19·2, ribs 19·1, femur 14·5, humerus 9·3, innominate 6·5, clavicle 4·2, scapula 1·2, leg-bones 0·9, forearm bones 0·45, and sternum 0·45.

[5] Inguinal 8·6, retro-peritoneal 8·3, bronchial 1·7, mediastinal 0·4.

[6] No doubt instances of direct lymphatic extension are comprised under this heading.

uterus 3·1, pancreas 2·5, thyroid 2·5, heart 1·6, muscles 0·9, bladder 0·7, omentum 0·6, Fallopian tube 0·5, venous system 0·4, spinal medulla 0·4, facial nerve 0·4, vagina 0·2, œsophagus 0·1 and ureter 0·1.

Metastases, secondary to cancer of the breast, have also been met with in he uveal tract—especially in the choroid;[1] and mammary cancer has even been known to disseminate in a uterine myoma (Bender and Lardennois[2]).

In mammary cancer, as I have previously mentioned, the ribs, sternum, and occasionally the clavicle, and even the upper end of the humerus may become cancerous, through direct extension of the primary disease or through its local dissemination: such cases have been excluded from this list, whenever there was sufficient information to warrant it.

S. Coupland[3] has described a case in which the metastases were limited to both ovaries; Colle and Paquet[4] to the liver; Cruveilhier,[5] Walther,[6] Letienne,[7] Arnott,[8] and Hillier,[9] to the osseous system.

Of 40 intra-cranial metastases in Török and Wittelshöfer's analysis, the parts affected were: dura mater in 25, cerebrum in 22, cerebellum in 13, pia mater in 3,[10] and pineal body in 2 cases.

It is noteworthy that the incidence of metastases in cancer of the *breast*, in *males*, is similar to that which we have seen holds in the case of females: thus, of 10 necropsies analysed by me, there were metastases in 7, or in 70 per cent. These were located as follows:—in the liver, 3 cases, lungs and pleura (both 2, right 1) 3 cases, bones 3 cases, kidney (both) in 1 case, bladder 1, peritoneum 1, stomach (cardiac end) 1, and pancreas in 1 case. The following were the bones involved:—both clavicles and tibia in 1 case, vertebræ and other bones in 1 case, and the sphenoid with the base of the skull in 1 case.

The following analyses give a good idea of the relative frequency and site-incidence of metastases, secondary to cancer of the *cervix uteri*.

Of 79 consecutive necropsies, I found that dissemination had taken place in 16, or in 20·2 per cent.; thus the cervix uteri is one of those parts, in which the liability of cancer to disseminate in distant localities is not very great. The probable explanation of this difference is, that patients with cancer of the cervix are commonly cut off by fatal intercurrent complications, before the cancerous disease has had time to mature; for this form of dissemination seldom sets in, until a comparatively late stage of the disease. It accords with this, that metastases are of more frequent occurrence with cancer of the corpus uteri,

[1] Of 31 metastatic choroidal cancers tabulated by H. Parsons, in 24 the primary cancer was mammary.

[2] *Bull. et Mém. Soc. Anat.*, Paris, October, 1904.

[3] Transactions of the Pathological Society, London, vol. xxvii., p. 26; for a somewhat similar case by Nadig, *vide Rev. de Gyn. et de Chir. Abd.*, January and February, 1903.

[4] *L'Écho Méd. du Nord*, 1906, No. 23, p. 160: it was thought to be a case of primary multiplicity.

[5] *Vide* my book on "Diseases of the Breast," p. 200.

[6] *Ibid.*

[7] *Bull. Soc. Anat.*, Paris, 1890, p. 425.

[8] Transactions of the Pathological Society, London, vol. xix., p. 356.

[9] *Archives of the Middlesex Hospital*, vol. iii., p. 122.

[10] For instances of dissemination in the cerebral and spinal meninges, peripheral nerves etc., *vide* Peabody (Transactions of the Association of American Physicians, 1907, vol. xxii., p. 17).

when the average duration of the patient's life is considerably longer, than in the cervical form of the disease.

The seats of these metastases were as follows :

| | | |
|---|---|---|
| Lungs (both 6, right 1) .. .. .. .. .. | in | 7 cases. |
| Liver .. .. .. .. .. .. .. | ,, | 7 ,, |
| Peritoneum and omentum .. .. .. .. | ,, | 4 ,, |
| Pleura (both 1, right 1) .. .. .. .. .. | ,, | 2 ,, |
| Skin of chest and abdomen .. .. .. .. | ,, | 1 case. |
| Tibia (right) and innominate bone (right) .. .. | ,, | 1 ,, |
| Heart .. .. .. .. .. .. .. | ,, | 1 ,, |
| Kidney (left) .. .. .. .. .. .. | ,, | 1 ,, |
| Ureter (left) .. .. .. .. .. .. | ,, | 1 ,, |
| Bronchial glands .. .. .. .. .. .. | ,, | 1 ,, |

Dissemination in the bones is rare in uterine cancer ; but, in addition to the case included in the foregoing analysis, I know of instances in which it has occurred in the femur,[1] humerus,[2] and ribs [3] respectively.

Of 187 similar necropsies, analysed by Andriezen and Leitch,[4] metastases were found in 20·4 per cent.

Their site-incidence and percentage distribution were as follows :—liver 13·5, lung 6, peritoneum 5, kidney 2·6, supra-renal 1·9, pleura 1·4, heart 1, bones [5] 0·9, stomach and intestines 0·9, pancreas 0·9, diaphragm 0·7, gall-bladder 0·6, abdominal wall 0·4, thoracic wall 0·3, subcutaneous 0·3, pericardium, thyroid, œsophagus and mamma of each 0·1.

Other parts sometimes implicated by the dissemination of this form of cancer are the brain, dura mater and skin.

Of 33 necropsies, by the same authors, for cancer of the *corpus* uteri, metastases were met with in 15, or in 48·5 per cent. : the seats of these lesions were—the liver (15 per cent.), lungs (15 per cent.), intestine (12 per cent.), spleen, pericardium, pleura, diaphragm and ribs (each in 3 per cent.). The peritoneum was involved in 27 per cent. of these cases.

Schiller [6] has lately reported an instance of metastatic cancer of both knee-joints, which supervened eight weeks after abdominal hysterectomy for this kind of cancer.

Of 10 necropsies for cancer of the *prostate,* analysed by Walker,[7] metastases were noted in 6 ; the parts affected being the liver in 3, and the lungs in 3 cases—while the pancreas, adrenal, kidneys, testis, peritoneum and colon, were also involved, each in 1 case.

It is noteworthy that, in this series, not a single example of dissemination in the osseous system was found ; yet, according to Kaufmann

[1] St. Bartholomew's Hospital Report, 1888, p. 389 : " Cancer of cervix uteri, with dissemination in the left femur."

[2] University College Hospital Report, 1888, pp. 92 and 142 : " Cancer of the cervix uteri, with dissemination in the upper part of the right humerus, which was mistaken for primary sarcoma, for which the upper limb was amputated at the shoulder-joint " ; *vide* also Transactions of the Pathological Society, 1886, vol. xxxvii., p. 379, for what appears to be a similar case.

[3] " Catalogue of the Middlesex Hospital Museum," p. 69, No. 600 : " Cancer of the cervix uteri with dissemination in the ribs."

[4] " Archives of Middlesex Hospital," 1906, vol. vii., p. 165.

[5] The bones implicated were—vertebræ. 2 cases ; innominate, 2 cases ; skull, ribs, and tibia of each 1 case. Billroth and Leucke found metastases in the bones in 5 of their 166 uterine-cancer necropsies, or in 3 per cent.

[6] *Monats. f. Geb. u. Gyn.*, June, 1907, S. 953.

[7] " Archives of Middlesex Hospital," 1905 vol. v., p. 157.

and others, prostatic cancer disseminates in the bones in from 13 to 70 per cent. of all cases. But, spontaneous fractures and other noticeable lesions, seldom result ; so that these metastases may easily be overlooked, unless the skeleton is specially examined *ad hoc*, and this explains the divergences in the estimates as to its frequency. Thus Kaufmann found osseous metastases in 34 per cent. of the cases reported in the post-mortem records ; but of 22 cases, in which the bones were specially examined, intra-osseous metastases were found in all but four.

The seats of these osseous metastases, in order of relative frequency are :—the vertebræ, os innominatum, femur, ribs, sternum, skull, humerus, tibia, scapula, clavicle, fibula, and bones of the forearm.

In further illustration of this subject, I propose to examine the site-incidence and relative frequency of metastases ; in the chief local varieties of epithelial cancer, throughout the *alimentary system*.

In the *lower lip* epithelial cancer rarely gives rise to metastasis ; for, of 13 consecutive necropsies many of which were made by myself, this form of dissemination was met with in only 2 cases, or in 15·4 per cent. The parts thus invaded were, the lungs (right 1, left 1) in 2 cases, and the kidney (right) in 1 case.

Of 57 consecutive necropsies for epithelioma of the *tongue and mouth* analysed by me, metastases were found in 7, or in only 12·3 per cent. The parts thus affected were the liver and both lungs in 2 cases, both lungs in 2 cases, the liver, left kidney and mesenteric glands, each in 1 case.

In the *tonsil* this type of cancer seems to cause metastases with great frequency ; for, of 3 necropsies in Butlin's [1] list, all disseminated—1 in the liver, 1 in the lungs and 1 in the thyroid.

In the *œsophagus* epithelial cancer often disseminates ; thus, of 14 consecutive necropsies some of which were made by myself, lesions of this kind were found in 5, or in 35·7 per cent., the parts affected being the liver in 2 cases, peritoneum 2 cases, kidney (right), lung (right), and bladder, each in 1 case. In 2 of these cases the disease spread by continuity from the œsophagus to the stomach,[2] in 5 cases to the trachea, in 3 to the bronchus, in 2 to the lung and pleura, and in 2 to the pharynx.

Of 15 similar necropsies, N. Moore [3] found metastases in the liver in 7, lungs in 5, kidney in 4, and the pancreas, spleen and adrenal each in 1 case.

Other localities in which metastases have been met with are, the brain and its membranes, skin, and the osseous system (vertebræ, femur and sternum).

The stomach, peritoneum, adjacent vertebræ, thyroid, larynx, heart and pericardium, are fairly often invaded by direct extension.

In cancer of the *stomach*, says Brinton,[4] " the liver is involved in a

[1] " Sarcoma and Carcinoma," 1882.

[2] Secondary cancer of the stomach is a very rare affection, except when some adjacent part of the digestive tract is the seat of primary cancer. Most cases of this kind are secondary to primary cancer of the œsophagus. Thus of 25 cases of secondary gastric cancer tabulated by Castro, in 18 the source of the primary disease was in the œsophagus. Of the 7 cases in which the primary disease was situated outside the digestive tract, the localities affected were, the female breast in 3 cases, the eye, tongue, testis, and leg—each in 1 case.

[3] *Lancet*, 1889, vol. ii., p. 417.

[4] " Diseases of the Stomach," p. 245.

ratio twice as great as that of such deposit in the adjacent lymph-glands, and thrice as great as that of secondary cancer of the lungs." In the light of recent researches, Brinton certainly under-estimated the frequency of lymph-gland dissemination in gastric cancer; and the same may be said of Gussenbauer's analysis,[1] in which dissemination in the adjacent lymph-glands was noted in 273 of 903 necropsies, or in 30 per cent.[2]

In the latter analysis, dissemination was found in 572 of the total necropsies, or in 63·3 per cent.—the liver being the part involved in 259 (28·6 per cent.), the pancreas in 100 (11 per cent.), and the peritoneum, omentum, and intestines in 173 (19 per cent.).

Brinton estimated the frequency of dissemination in gastric cancer, at 48 per cent. of the total necropsies, and Lebert at 40·9 per cent. According to Lebert, the peritoneum was invaded in 37·5 per cent., the liver in 25 per cent., the lungs in 8·3 per cent., and the ovaries in 4·5 per cent.

In gastric cancer, the liver and adjacent structures are no doubt very frequently invaded by direct extension of the disease by the lymphatics etc.; and Gussenbauer notes that the stomach was matted to neighbouring structures, in 394 of his 903 necropsies.

In N. Moore's[3] careful study of 29 gastric-cancer necropsies, in only 3 cases was the disease limited to the stomach. He notes its frequent spread by continuity (in 7 cases), along the lymphatics in the vicinity of the upper and lower borders of the stomach, to adjacent structures, *e.g.*, to the liver, in 4 cases; to the diaphragm, omentum, mesentery, pancreas and transverse colon—each in 2 cases; and to the œsophagus, ascending colon, spleen, vertebræ, and inferior vena cava—each in 1 case.

Dissemination in the lymph-glands of the hilum of the liver, lumbar, mesenteric and mediastinal regions, was noted in about 60 per cent. of the total necropsies.

Besides these lesions, metastases were found in the liver in 2 cases; and in the heart, spleen and adrenal—each in 1 case.

The latest research into this subject, by Colwell,[4] shows that of 115 necropsies for cancer of the pyloric region of the stomach, metastases were noted in 81, or in 70·4 per cent., the site incidence of these lesions being as follows:—liver in 47 cases, peritoneum in 29, pancreas 6, pleura 5, lung 5, ovary 3, adrenal 3, heart 2; pericardium, intestine, spleen, thoracic duct, skin, ribs and vertebræ—each in 1 case.

The liver was also invaded by the direct extension of the primary disease, in 23 cases, and the pancreas in 16 cases.

The following lymph-gland dissemination was noted:—portal glands in 50 cases, cœliac in 30, mesenteric in 25, aortic in 20, mediastinal in 3, and axillary in 1 case.

Gastric cancer has been known to disseminate in the choroid,[5] the uterus,[6] the brain, and the skin. Risel[7] has lately described two

[1] *Arch. f. klin. Chir.*, 1876, Bd. xix., S. 372.
[2] For further details, *vide* p. 417 of this chapter. [3] *Lancet*, 1889, vol. ii., p. 418.
[4] "Archives of Middlesex Hospital," 1906, vol. vii., p. 151.
[5] H. Parsons, "Pathology of the Eye," 1905, vol. ii.
[6] *C. R. Soc. d'Obstét. de Gyn.*, etc., Paris, May, 1905 (Couvelaire).
[7] *Ziegler's Beitr. z. path. Anat.*, etc., 1907, Bd. xlii., Heft 2.

remarkable cases of gastric cancer, in which the disseminative lesions resembled "chorio-epithelioma."

Dissemination in the skeletal system is rare, since only three instances of it[1] were noted in 174 consecutive necropsies analysed by Colwell, or in 1·7 per cent.; and not a single example of it is mentioned by the other authors above cited. Cruveilhier,[2] however, long ago described an instance, in which the disease disseminated in the right humerus (with spontaneous fracture) and sternum, there being no other metastases. Perry and Shaw[3] have also found cancer of the pylorus, with spontaneous fracture of the femur owing to cancerous metastases—the liver and lungs also being similarly affected. Recently other instances of this kind have been published by Kurpjuweit,[4] Goetsch,[5] Zade,[6] Pinatelle and Cavaillon.[7] In Goetsch's case, the osseous system was extensively invaded—the cranium, vertebræ, ribs, sternum, clavicle and pelvic bones being affected, as well as the dura mater: in the other cases, the bones invaded were the third lumbar vertebra, base of skull and left parietal bone—each in 1 case.

Colwell's analysis shows that ovarian dissemination is rare in gastric cancer; since but five examples of it were noted in 174 consecutive necropsies, or rather less than 3 per cent.; and the other above-cited analyses are of similar import.[8]

Of late, however, a considerable number of cases have been reported in the medical periodicals, of bilateral, large, solid ovarian tumours—the so-called "Krukenberg's tumours"—concomitant with gastric cancer. It is to Schlagenhaufer[9] and Wagner[10] that we are specially indebted for showing, that these tumours are sometimes due to cancerous dissemination from a primary focus, the usual seat of which is in the stomach, the intestines or elsewhere. They had previously been regarded as independent new formations of endotheliomatous, fibro-sarcomatous or fibroid nature. Of 79 cases of this kind tabulated by Schlagenhaufer, in 61 the primary focus was in the stomach, in 10 in the intestine, and, in the other 8 cases, in various intra-abdominal situations.

It yet remains to be proved whether most cases of "Krukenberg's tumours," concomitant with a malignant focus elsewhere, really are of metastatic nature; or, whether most of them may not be of independent origin—bearing the same ætiological relation to the concomitant cancerous focus, that bilateral ovarian cystic disease often seems to have to "chorioma malignum."

Of 17 necropsies for epithelial cancer of the *colon*—9 by N. Moore and 8 of my own series—metastases were found in only 4 cases, or in 23·5 per cent.: the parts affected being the liver alone in 3 cases, the liver and lungs (both) in 1 case. In 12 of these necropsies the disease

[1] Vertebræ, 2 cases; ribs, 1 case. [2] *Anat. Path.*, liv. xx., p. 5.
[3] Guy's Hospital Report, 1891, vol. xlviii., p. 155 (Case 21).
[4] *Deutsche Arch. f. klin. Med.*, 1903, Bd. lxxvii., S. 552.
[5] *Ziegler's Beitr. z. path. Anat.*, etc., 1906, Bd. lxxxix., S. 218.
[6] *Ibid.*, 1904. [7] *Prov. Méd.*, April 14, 1906.
[8] When cancerous disease of the stomach penetrates the gastric wall, it may disseminate throughout the peritoneal sac by auto-implantation, invading the ovaries, uterus etc., as in cases reported by Schenk, to which I have previously referred.
[9] *Monatschr. f. Geb. u. Gyn.* (supplement), April, 1902, Bd. xv.
[10] *Wien. klin. Woch.*, 1902, Bd. xv., No. 20, S. 519.

had spread by direct continuity to adjacent structures, as follows:—ileum in 3 cases, duodenum 3 cases, one ovary in 2 cases, stomach 2 cases, other parts of colon 2 cases, abdominal wall 2 cases; and to the uterus, bladder and liver—each in 1 case. Dissemination in adjacent lymph-glands, was noted in 5 of the 17 necropsies.

In cancer of the *rectum* metastasis is of much more frequent occurrence, since of my 27 consecutive necropsies, this form of dissemination was met with in 14, or in 51·5 per cent.; the parts affected were, the liver in 12 cases, lungs (both 4, left 1, right 1) in 6 cases, kidney (both) in 3 cases, spleen in 2 cases, pleura (both), ovary (both), mamma (left), adrenal (right), dorsal vertebræ (seventh and eighth) and ribs—each in 1 case.

The adjacent structures were invaded by direct extension in 20 of these 27 necropsies, as follows:—pelvic connective tissue in 14 cases, peritoneum in 10 cases, bladder in 8 cases, vagina and portio in 5 cases (of 12 necropsies in females), omentum and pelvic bones—each in 1 case.

The adjacent lymph-glands were obviously invaded in 17 of 21 necropsies.

Besides the case in the foregoing series, in which the disease disseminated in the dorsal vertebræ and ribs, I know of several other instances of this kind, *e.g.*, in the right humerus by Pitts [1] (with spontaneous fracture); in both innominate bones, both tibiæ, eighth, tenth and eleventh dorsal vertebræ, right parietal bone and basis cranii, as well as in the liver, one lung and the intra-abdominal lymph-glands by Gowers; [2] in the left femur, liver and lung by Fuzinami; [3] and by Goetsch [4] in the sternum, first, second, and seventh ribs, cranium, vertebræ and right femur, as well as in the liver, lungs, right kidney and retro-peritoneal glands.

Of 11 necropsies for cancer of the *pancreas*, N. Moore [5] found metastases in 7, or in 63·6 per cent., the liver being involved in 6, the lungs and kidneys each in 2 cases, the peritoneum and heart each in 1 case. In 3 cases adjacent parts were invaded by direct extension, viz., the stomach, gall-bladder and transverse colon in 1 case, the duodenum in another, portal fissure and its lymphatics in the third case.

In epithelial cancer of the *ovary* metastases are of very frequent occurrence; for, of my series of 9 consecutive necropsies, lesions of this kind were noted in 8, or in 88·8 per cent., the parts affected being the liver in 5 cases, peritoneum 5 cases, lung (right) in 2 cases, great omentum 2 cases; pleura, pericardium, pancreas, kidney (left), intestine, mamma (right), bladder, heart, and skin—each in 1 case.

The following parts were also invaded by direct extension of the disease: uterus in 4 cases (with Fallopian tube in 2), peritoneum in 3 cases, rectum, right ureter and kidney—each in 1 case.

Of 4 necropsies for malignant epithelial tumours of the *testis*, Butlin [6] found that metastases had taken place in every case, as follows:—(1) liver, lungs and right breast; (2) liver and lungs; (3) adrenal; (4) omentum.

[1] Transactions of the Pathological Society, London, 1891, vol. xlii., p. 267.
[2] *Lancet*, 1905, vol. ii., p. 1593.
[3] *Arch. f. path. Anat.*, 1897, Bd. cxlvii., S. 129.
[4] *Ziegler's Beitr. z. path. Anat.*, etc., 1906, Bd. lxxxix., S. 218.
[5] *Op. cit.*
[6] "Sarcoma and Carcinoma," 1882.

In every case there was dissemination in the adjacent lymph-glands.

Of my 6 necropsies for cancer of the *bladder*, metastasis was noted in only 1—there being a single, small, cancerous nodule in the right lobe of the liver.

In 3 cases the adjacent parts were invaded by direct extension, viz., the pelvic connective tissue in 2 cases, and the left ovary in 1 case.

S. Cooper has known this local variety of cancer disseminate in the left femur (with spontaneous fracture), and in the fifth right rib.

## The Metastases of Sarcomatous Tumours.

Of 91 necropsies for sarcoma of the *female mamma* tabulated by Gross,[1] metastases were found in 17, or in 18·68 per cent.; and of 40 similar cases by Schuoler,[2] in 12·4 per cent.

As Gross has pointed out, the liability to metastasis varies with the structure of the primary tumour, the percentage figure being 25 for the round-celled variety, and 20·4 for the spindle-celled; while none of the myeloid forms disseminated.

In Gross' cases the metastatic tumours were located as follows:—lungs in 10 cases, liver in 4, brain in 3; and 1 each in the dura mater, retro-peritoneal glands, mediastinum, pleura, heart, kidney, muscles and bones.

Of 8 necropsies for this malady by Campiche and Lazarus-Barlow,[3] metastases were noted in the liver in 4 cases, pleura in 3, kidneys in 3, brain in 2; and 1 each in the pericardium, stomach, intestines, mesentery, sternum, lungs and adrenal.

In a case recorded by Virchow,[4] the disease disseminated in the lungs, liver, mediastinum, ribs, vertebræ, pelvic bones, dura mater and sphenoid. Delbarre[5] has seen round-celled mammary sarcoma, associated with similar ovarian disease.

Of 8 necropsies in my list, for sarcoma of the *superior maxilla*—only 3 of which were myeloid—none originated metastases. In one of these cases, the disease had spread by direct extension, through the sphenoidal fissure into the middle fossa of the skull, where it formed a tumour—the size of a walnut—which compressed the brain.

According to Gross,[6] metastases are met with in 64 per cent. of all necropsies for sarcoma of the *long bones*, the relative frequency of these lesions varying with the kind of tumour, being greatest for the periosteal forms (100 to 65 per cent.), less for central tumours (33 to 23 per cent.), and least of all for the myeloid form (22 per cent.). The site incidence of metastases is shown by the following analysis of 30 necropsies, in which periosteal forms predominated:—lungs (generally both) in 25 cases, bones in 12, distant lymph-glands (chiefly bronchial) in 8, pleura in 5,

[1] *International Journal of the Medical Sciences*, 1887, p. 17.
[2] *Corresp. Bl. f. schw. Aerzte*, 1890, S. 283.
[3] "Archives of Middlesex Hospital," 1905, vol. v., p. 112.
[4] *Path. des Tumeurs*, t. ii., p. 360.
[5] *Bull., etc., de la Soc. Anat.*, 1870, p. 337.
[6] *American Journal of the Medical Sciences*, July and October, 1879.

diaphragm in 3, kidney in 3, pericardium in 2, brain in 2, liver in 2; omentum, spleen, subcutaneous tissue, inferior vena cava and muscles—each in 1 case.

Of 22 cases of sarcoma of the *femur*, by Butlin and Colby,[1] there was dissemination in the lungs in 7, kidney in 2, bones in 2; diaphragm, ureter, and pleura—each in 1 case.

Of 13 cases of sarcoma of the *tibia* by the same authors, metastases had formed in 2—the lungs, ribs, clavicle, skull and femur being invaded in 1 case; and, in the other, the lungs, pleura, pericardium and various bones.

Sarcomatous tumours of the *choroid* and uveal tract—which are mostly of the melanotic kind, and of round- spindle- or mixed-cell type—are exceedingly prone to form metastases. Unfortunately, none of the extensive and elaborate analyses that have been published, enable me to state exactly in what proportion of fatal cases metastases are met with; but, from the general tenor of these reports, it may be inferred that metastases are of almost invariable occurrence. This is the usual cause of death after extirpation of the globe etc.; for local recurrence is comparatively rare. Some idea of the great frequency of metastasis may be gathered from the fact, that of 243 operated cases tabulated by Fuchs,[2] only 6 per cent. were alive and well four years after the operation. Of Lawford and Collins' 79 operated cases, however, 25·3 per cent. were alive and well three years and upwards after extirpation. A curious feature about the metastatic recurrence of these choroidal sarcomata is, that they are just as frequent after early, as after late extirpation of the eye; although local recurrence is much rarer, when early operation is resorted to. It is also interesting to note, that the secondary tumours are not invariably pigmented, when the primary tumour is thus characterized.[3] As previously mentioned, choroidal sarcoma hardly ever disseminates in adjacent lymph-glands.[4] It is generally considered that the soft, cellular, and vascular forms of choroidal sarcoma, have the greatest proclivity to disseminate by metastasis. Of the parts thus implicated, the liver is the one most frequently mentioned; other parts apt to be affected are the kidneys, stomach, lungs, heart, skin, bones, intestines, muscles, and very rarely the serosa, the spinal and cranial cavities.

With *glioma of the eye*, metastases are of very much rarer occurrence,

[1] St. Bartholomew's Hospital Report, 1895, vol. xxxi.

[2] *Das Sarcom des Uvealtractus*, Wien, 1882.

[3] J. H. Parsons has reported an instance in which a melanotic sarcoma of the choroid, with an unpigmented intra-ocular extension, caused death by metastasis in the liver one and a half years after extirpation of the affected eye, when several ribs, the lung and mediastinal glands, were found to be invaded by secondary growths having the structure of squamous-celled epithelioma (*Lancet*, 1904, vol. ii., p. 1421).

[4] Referring to this, Juler says (*Handb. Ophth. Sci.*, p. 153):—"In many cases the tissues outside the sclerotic are affected by the new growth, while the tumour inside the globe is quite small; in these cases the cells pass to the outside by means of the sheaths of the bloodvessels, which are seen to be thickened and altered by the presence of cells similar in character to those of the tumour. . . . The neighbouring lymphatic glands are not affected; but secondary sarcoma is liable to be set up in distant parts, the cells being conducted from this primary source by means of the blood current." In view of the incongruities thus indicated, is it not more probable that the tumour-cells emerge from the globe, *within* the bloodvessels, rather than in their external sheaths, as the appearances seem to indicate?

than with sarcoma of the choroid; while lymph-gland dissemination is commoner. I have seen glioma disseminate in the dura mater, and in the right deltoid muscle; and Knapp,[1] in the liver, lungs and cranial bones. Metastasis has also been known to involve the kidney, ovary, sternum and ribs. In cases of this kind, Bizzozero and others have found glia cells in the blood.

Of 13 necropsies for sarcoma of the *testis*, in Butlin's [2] analysis, metastases were found in 11, or in 84·6 per cent., the parts invaded being as follows:—lungs in 7 cases, bones in 3, heart in 3, subcutaneous tissue in 2, kidney in 2; and in the liver, skin, penis and spleen—each in 1 case. There was lymph-gland dissemination, in 11 of 14 fully examined cases.

Of 50 fatal cases of *deciduoma malignum vel chorio-epithelioma*, tabulated by me, metastases were found on post-mortem examination in 41, or in 82 per cent.; the percentage site incidence was as follows:—the lungs in 72, brain 20, kidney 18, spleen 16, liver 14, intestine 12, heart 10; mesentery, bronchial glands, bones and stomach—each in 4 per cent.; pancreas, pulmonary and hepatic veins, omentum and thyroid—each in 2 per cent.

The following adjacent structures were also involved:—vagina in 44 per cent.; other parts of the uterus than that occupied by the primary focus, in 20; one or both ovaries, in 14; peritoneum, in 12; both broad ligaments, in 8; pelvic connective tissue, in 4; bladder and abdominal wall—each in 2 per cent.

In these same cases there was dissemination in the adjacent lymph-glands, only in 5 cases, or in 10 per cent.

Thus this anomalous form of malignant tumour in its metastases, as in its lymph-gland dissemination, manifests more similitude to sarcoma than to epithelioma.

## General Conclusions.

Reviewing the whole subject in the light of the foregoing facts, it appears that all kinds of dissemination—local, glandular and metastatic—are of less frequent occurrence with sarcomatous, than with malignant epithelial tumours; this peculiarity being most marked in respect to lymph-gland dissemination. The alleged frequency of lymph-gland dissemination with sarcoma of the tonsil and testis, is not based on a sufficiently large number of duly authenticated cases, to rank as an ascertained fact. As for the other apparent exception to this rule, melanotic sarcoma of the skin, most pathologists now consider the majority of these tumours, to be of epithelial origin.

Myeloid sarcoma, like rodent ulcer, seldom originates any kind of disseminative lesion.

The only other epitheliomatous tumour, with which lymph-gland dissemination is not of frequent occurrence, is the so-called "chorio-epithelioma"—the affinity of which with sarcoma, is clearly indicated by all its disseminative manifestations. In this form of malignant disease, as in periosteal sarcoma of the long bones, metastatic dissemination is of the greatest frequency.

[1] *Die intraocularen Geschwülste*, 1868. [2] *Op. cit.*

Another important feature indicated by our analysis of the data of dissemination is, that for all epithelial malignant tumours, the *liver* is the organ most frequently the seat of the metastasis; whereas, for sarcomata, the *lung* is the commonest seat of these lesions.

With regard to the malignant epithelial tumours, the only apparent exception to this rule is in the case of thyroid; but, thyroid sarcomata often comprise epithelial elements, blended in such a way as to make the discrimination from epithelioma by histological examination practically impossible, as I have previously mentioned. Owing to this cause, no doubt many adeno-sarcomata have been classed in Ehrhardt's tables, as epitheliomata. This is but another example of the importance of metastatic manifestations, as an element in the problem of the diagnosis of the type of malignancy, for which the histological appearances *per se* are so often inadequate.

In the case of sarcomata, the only apparent exception to our rule of the lung being the commonest seat of metastasis, is to be found in the choroid, where the liver is generally credited with this distinction; but, as to this, there is at present lack of precise numerical details. Besides, is it absolutely certain—in view of Parsons' previously cited case, and of other indications of similar import—that all melanotic choroidal malignant tumours, are of connective-tissue origin ?[1]

With regard to intra-osseous metastases, although both types of malignant disease not infrequently cause them, there can be no doubt that they are of commoner occurrence with the epithelial type of tumour, than with its connective-tissue counterpart. With the latter type of malignant disease this form of metastasis is most frequent, when the primary localization is skeletal; and, even with epithelial cancer, the commonest precursor of intra-osseous dissemination often is the invasion of some bone adjacent to the primary cancer, by direct extension of the latter, such for instance, as the sternum, ribs, clavicle or upper end of the humerus, when the breast is the original seat of the disease.

As may be gathered from what has already been stated, recent experience shows that dissemination in the bones is of much more frequent occurrence than has hitherto been supposed, several of those who have specially examined the subject having found intra-osseous metastases in from 20 to 25 per cent. of all cancer necropsies (E. Fraenkel, Fischer-Defoy etc.). Intra-osseous lesions of this kind comparatively seldom cause obvious external deformity; hence, unless the skeleton is specially examined *ad hoc*, such lesions usually escape notice. No cancer necropsy ought to be considered as complete, without special examination of the skeleton.

Some remarkable differences in the proclivity of malignant tumours of particular localities to disseminate in the bones are noticeable. I have already referred to the great frequency of such occurrences when the primary disease is situated in the prostate, thyroid, mamma and skeletal bones; and to its decided rarity when the initial lesion is of cutaneous, labial, buccal. lingual, intra-ocular, uterine or gastric origin;

[1] For some pertinent remarks on this subject by Lawford, *vide British Medical Journal*, 1892, vol. ii., p. 84.

while, when the rectum or œsophagus is the part affected, intra-osseous dissemination is not of such exceptional rarity.

Lately Scudder[1] has called attention to the frequency with which a certain type of renal malignant tumour (hyper-nephroma) disseminates in the bones; and R. Hutchison[2] has collected many instances of this kind secondary to supra-renal "sarcoma" of early life.

### The Theory of Metastasis.

By far the most feasible explanation known to me of the phenomena of metastasis, is that furnished by the "embolic theory." This implies that the germs whence metastases arise are proliferous cells, detached from the primary neoplasm, or its derivatives; and carried off by the blood-stream. These, by their continuous proliferation, directly originate the secondary growths; so that the first cancer is the parent of all that form after it. The conception of metastasis, as due to specific virus (blastema etc.) dissolved in the blood, belongs to old humoral pathology; and now finds no support, except with those who would revive the old doctrine, in connexion with the microbic theory.

According to Nepveu,[3] the veritable agents of dissemination, are not the cancer cells themselves—for these are generally too large to pass through the capillaries — but their young offspring (*seminium cellulaire*), which penetrate everywhere. These minute bodies he claims to have found in the blood of the tumour and its vicinity, as well as in the general circulation.

It accords with this conclusion, that the only structures in which metastases are never found, are avascular parts, like cartilage and cornea, which are permeable to fluids, but not to cells.

Friedreich's[4] case of cancerous dissemination in the skin over the left knee of a fœtus—whose mother died during pregnancy with cancer of the liver, and multiple disseminative nodules in the uterus, mammæ, bones, intestines etc.—much relied upon by the advocates of infection by the fluids, as supporting their theory, can be accounted for by the embolic theory. We know from Porak's researches, that foreign substances may pass through the placenta, although as a rule there is no mixing of fœtal and maternal blood. The permeability of the placenta to microbes, has also been demonstrated. Hence we may infer that young cancer cells, which often are exceedingly minute, may also pass through the placenta.

In the first chapter of this work, I indicated that each of the constituent phenomena of malignancy—including metastasis—has its physiological prototype. Before proceeding further with the development of our rationale of metastasis, it seems desirable here to discuss briefly its physiological prototype.

[1] "Publications of Massachusetts General Hospital," Boston, U.S., 1907, vol. i., No. 3, p. 82.
[2] *Quarterly Journal of Medicine*, 1907, vol. i., No. 1.
[3] *Rev. des Maladies Cancéreuses*, October 20, 1895, p. 7.
[4] *Arch. f. path. Anat.*, Bd. xxxvi., S. 465.

It is a curious fact, that in the phases of placentation, all the phenomena of malignancy find their counterparts. Pathologists have often remarked on the similarity between the early stages of placenta formation—when the maternal tissues are invaded and interpenetrated by foreign epithelial ingrowths—and the cancerous process; and, by some, the placenta itself has been regarded as a kind of "physiological tumour." Under normal circumstances, these infiltrating processes, are, of course, confined within strict limits; and this it is which constitutes the distinction from malignancy.

As long ago as 1893, Schmorl[1] found that portions of the chorionic villi and cellular fragments thereof, were freely shed into the maternal circulation in puerperal eclampsia; and, in 1901, Veit[2] and others showed that similar occurrences are usual in the majority of normal pregnancies. These "deported" elements have great power of wandering; and, by their own vitality, are capable of penetrating the maternal bloodvessels and lymph-spaces. Usually, however, such emigrants are soon dissolved by the maternal blood, and completely disappear.

But, under certain abnormal circumstances, as yet not fully understood, these "deported" chorionic elements—instead of being absorbed—grow into tumour-like formations, of malignant or non-malignant character, according to the dynamical qualities elicited. The kind of fœtal lesion which specially predisposes to this disease, is the hydatidiform mole, now generally regarded as a chorionic tumour, with malignant and non-malignant varieties. It seems possible, however, that these chorionic tumours may exceptionally arise, even in the absence of any recognizable primary neoplastic focus in the chorion, or elsewhere; however this may be, it is a certain fact that more than half of those with chorionic tumours, have been the subjects of previous "mole" pregnancy. Just as it is impossible to draw a sharp line of distinction between the malignant and non-malignant varieties of "mole"; so likewise it is impossible to draw any such distinction between the benign and malignant varieties of "chorioma."

Now the question arises, how is it that these "deported" chorionic elements, survive and grow into tumours in some cases, while in others they are completely absorbed? The indications at present available, especially the almost invariable occurrence of these tumours *post-partum*—after abortion, "mole" pregnancy, or other processes involving death or removal of the fœtus—all point to abnormal changes in the ovary as the determining factor, of which we have evidence in the frequent concurrence of cystic disease of the ovaries, with hydatidiform mole and with malignant chorionic tumours.

Owing to alterations of this kind and to the changes in the blood which they induce, the latter loses its normal power of dissolving the intruding chorionic cells (syncytiolysis); which, under these pathological circumstances, then acquire powers of abnormal growth, the various chorionic tumours being the consequence.

It is thus probable, that some alteration of the ovarian internal

[1] *Verschleppung der Choriozotten*, Leipzig, 1893.
[2] *Zeitschr. f. Geb. u. Gyn.*, Bd. xliv., S. 466.

secretion, is the dominant factor underlying the various pathological changes of which metastasis is the outcome; and, hence, may we infer that some such change in the internal secretion of the sexual glands—and even of other organs—plays a part in the determination of metastasis in general?

This conclusion certainly harmonizes with other indications to which I have previously referred, such as the frequency of malignant disease in castrated animals, and—in humanity—after the surgical removal of the ovaries, or in consequence of their impairment by disease or by congenital defect; and a similar indication is the coincidence of the greatest proclivity to cancer, with decline of reproductive activity, to which I have specially directed attention in a previous chapter.[1]

Whether this is the correct explanation of metastasis in general or not, the site-incidence of these formations and other phenomena of similar import, clearly indicate; that the formation of metastases is conditioned by other considerations, besides those of mere mechanical distribution.

Many observations indicate that cancer cells enter the blood-stream directly, through the bloodvessels—especially the small veins—as well as indirectly, through the lymphatics, Goldmann's[2] researches being of special significance in this connexion.

Here also we must bear in mind, as has lately been redemonstrated, that there are many direct communications between the lymphatics and venous radicles, through which the diseased cells may readily disseminate from the one to the other system (Leaf, Warthin—"hæmolymph glands" etc.) by a kind of short circuiting; and thus may be explained many apparent anomalies in the site-incidence of metastases.

The occurrence of metastasis, without any lymph-gland dissemination, which is usual with sarcoma, and less frequent with malignant epithelial tumours, is evidence of this; and my own belief is that, even with cancers of the epithelial type, metastasis often originates in this way. Thus, hardly ever can a malignant epithelial tumour of the mamma be examined, without finding its veins, and those of its vicinity, invaded by the disease. In the earliest stage, the venous wall becomes adherent to the neoplasm; then it gets infiltrated, and its external coat perforated.[3] In the next stage, the new growth projects more and more into the vein, covered only by the intima of the latter. This soon yields, and the neoplasm—in the form of a small fungus—then projects into the lumen; whence the growth may be detached *en masse*, or in minute fragments. Cancer emboli of this kind have frequently been found free in the blood, between the primary seat of disease and its derivatives, and the right side of the heart; and, even in the latter, and in the pulmonary artery—its main trunk and its smaller branches. A remarkable feature lately brought to light by the researches of Goldmann and Schmidt

[1] Chapter XV.

[2] *E.g.*, Goldmann (*Deutsche med. Woch.*, 1906, No. 41); also *Lancet*, 1907, vol. ii., p. 1237, etc.

[3] According to Goldmann, the tumour cells reach the wall of the vessel by way of the vasa vasorum.

is, that although the blood-stream may teem with cancer cells, there may be no evidence of metastatic tumour formation.

M. B. Schmidt's work[1] on the dissemination of malignant epithelial tumours, is a convincing demonstration of the spread of cancer elements by the blood-stream ; thus, in 15 of 41 cases examined, he found emboli, composed of cancer cells, in the smaller branches of the pulmonary arteries, although only a small proportion of these eventually developed into cancerous tumours.

Similarly Councilman has shown, by careful examination of very minute secondary growths in the liver, originating from primary foci within the portal area, that these are at first situated entirely within the portal capillaries. Many other observations of similar import might easily be cited ; thus, Goldmann[2] has specially shown how frequently the small veins of cancerous tumours are invaded, and he has found cancer cells free in the blood, as well as in intra-venous clots, and in the venous walls. In exceptional cases, even the arteries may be thus invaded ; and, in this way, sudden and extensive dissemination of the disease may, he believes, be brought about.

It is certainly a mistake to suppose, that when free cancer cells enter the circulation, they necessarily or usually cause clotting ; and also that cancer cells are unable to grow in blood-clot.

Loeb's remarkable experiments as to the cancer-like growth of epithelium in blood-serum and agar, as well as many other pathological observations to the like effect, contradict the latter ; while the presence of cancer cells in the circulation, and of cancerous formations in intravascular blood-clots, as noted by many observers, likewise contradict the former.

Then, how can we account for epidermoidal-celled cancer of the tongue, producing an epidermoidal-celled cancerous metastasis in the left adrenal, with no other general disseminative lesion, as described in a previously cited case by Arnott, except by the embolic theory ?

Examples of this kind may be multiplied almost indefinitely, *e.g.*, epidermoidal cancer of the skin of a limb, with epidermoidal cancer of the glottis, as reported by Chapuis ;[3] epithelial cancer of the bladder, with a single metastatic nodule of similar structure in the right lobe of the liver, and no other general disseminative lesion, as in a case I have seen etc.

Similarly, how can we account for metastatic cancer of the choroid of the eye, secondary to mammary cancer—of which over a score of cases have lately been reported—except by the embolic theory ?

And, is it not just the same, with such cases as that described by Schaper,[4] in which primary cancer of the lung disseminated in an interstitial uterine myoma ; and as that by Bender and Lardennois,[5] in which primary cancer of the female breast likewise disseminated in a uterine myoma—no other part of the uterus being invaded ; as well as in

[1] "Die Verbreitungswege der Karzinome," etc. Jena, 1903.
[2] *Op. cit.* ; and *Berlin klin. Woch.*, June 15, 1896, S. 549.
[3] *Lyon. Méd.*, March 1, 1896.
[4] *Arch. f. path. Anat.*, 1892, Bd. cxxix., S. 61.
[5] *Bull. et mém. de la Soc. Anat.*, Paris, October, 1904.

Friedreich's[1] case of metastasis in the left knee of a fœtus, whose mother died of cancer of the liver with metastases, during pregnancy.

Recklinghausen's[2] careful study of the minute anatomy of the intra-osseous dissemination of cancer, secondary to primary foci in the prostate, thyroid etc., is of similar import; for in all these intra-osseous lesions he was able to demonstrate, that the disease originated and spread in the medullary bloodvessels, where the circulation is comparatively slow.

Then, with regard to "chorioma malignum," do we not constantly find secondary growths loose within the veins of the uterus, vagina and adjacent parts; as well as in the ~~veins~~ BLOOD VESSELS of the lungs, brain, the large veins in the vicinity of the heart, the vena cava inferior, the pulmonary artery and its ramifications in the lungs, and even in the cavities of the heart itself?

To my mind all these occurrences and many others of similar import, which are constantly presenting themselves in connexion with the metastasis of cancer, are absolutely inexplicable without the aid of the embolic theory. Certainly, it is quite impossible to explain such occurrences on the basis of "lymphatic permeation"; which, for this reason, must be regarded as a far inferior working hypothesis to the embolic theory for interpreting the facts of metastasis.

We have now to inquire, what it is that determines the development of metastatic tumours, in certain localities, rather than in others. There can be no doubt that the dissemination of cancer emboli is regulated by the same mechanical conditions, which determine the distribution of ordinary emboli: from the veins at the root of the neck, they pass to the right side of the heart, and thence to the lungs; whence those small enough pass through the pulmonary capillaries, and so into the left side of the heart, and thence into the aortic system. It seems to follow from this—since the pulmonary capillaries are considerably smaller than most cancer cells—that the latter must generally be arrested first of all in the lungs; and this is just what the researches of Martin Schmidt[3] show actually takes place. Thus, of twenty-eight cases of metastasis investigated by him, in all of which the primary morbid focus was outside the portal system, epithelial cancer elements derived from this focus were found in the lungs in every case. He was able to determine that in thirteen cases these lesions were due to lymphatic dissemination, through the diaphragm to the pleura, by retrograde conveyance from affected bronchial glands etc. In all the other fifteen cases, emboli containing cancer cells were found in the smaller branches of the pulmonary arteries in the lungs. But, as we have already seen as the result of our post-mortem analyses, and as Schmidt's researches also show, cancerous metastases form in the lungs much less frequently than these emboli were found in them; hence it is evident, as Schmidt specially points out, that most of these cancerous emboli perish and are absorbed, failing to find in the lungs conditions favourable to their continued growth. Probably most of them, owing to antecedent degenerative changes, reach their destination more dead than alive. Thus, but few of these emigrant cancer cells survive, so as to originate secondary cancerous growths.

[1] *Arch. f. path. Anat.*, Bd. xxxvi., S. 465.
[2] *Festschr. zu Virchows* 71 *Geburtstag.* Berlin, 1891. [3] *Op. cit.*

When the initial morbid growth is of a sarcomatous nature, say a periosteal round-celled sarcoma of a long bone, no doubt the mechanism of lung metastasis is identical with the foregoing; but, in this case, the malignant connective-tissue cells—being differently constituted to their epithelial congeners—find in the pulmonary tissues a congenial habitat, in which they readily continue their morbid growth; so that secondary sarcomatous tumours frequently form, although in this case, as in the former, many of the emigrant cells certainly perish through degeneration.

Thus may the remarkable difference in the proclivity manifested by epithelial and connective-tissue malignant tumours, to form metastases in the lungs, be accounted for.

Hence I conclude that the diversities in the site-incidence of metastatic tumours, are not due to the cancer emboli being arrested only in certain selected situations; but rather, that all parts are exposed to their incidence in accordance with the ordinary laws of embolic distribution, secondary growths forming only in those localities, where they find suitable conditions. Thus, the differences in the site-incidence of metastases in sarcoma and epithelioma, in respect of the lungs, are not due to diversities in the distribution of the cancer emboli; but to the fact that, in the epithelial type of malignant disease, the arrested emboli comparatively seldom grow into secondary tumours.

Similarly may be explained the great proclivity of malignant epithelial tumours to form metastases in the liver, and the comparative rarity with which sarcomata disseminate in this organ; as well as the other diversities of site-incidence noticeable, between the metastases of malignant epithelial and sarcomatous tumours.

In like manner may also be interpreted the equally striking diversities, as to the site-incidence of metastases, between malignant tumours of the same type, of which our post-mortem analyses furnish so many examples; such as the frequency of metastases in the liver, secondary to epithelial cancer of the mamma, and the rarity of such disseminative growths in the spleen, although both organs are about equally exposed to the incidence of cancer emboli.[1]

Here also reference may be made to the singular immunity of the muscles of the body and some other structures from metastatic growths, whether secondary to a malignant focus of epithelial or connective-tissue origin; whence it may be inferred, that these tissues produce substances inimical to the growth of aberrant cancer cells in their midst.

That cancer emboli frequently survive and develop into secondary tumours, in spite of the resistance of the tissues, evidently must be due to their abnormal inherent activity, or to falling off in the physiological capacity for resistance of the tissues; and, in most cases, it seems certain that both of these factors are concerned.

From the foregoing it will be gathered, that the ultimate fate of a cancer embolus—its complete absorption or its development into a secondary cancerous growth—depends mainly upon whether the inherent

[1] Some of this diversity is no doubt due to direct extension of the mammary disease to the liver, as Handley has indicated.

vital activity of its constituent cells, is strong enough to resist successfully the disintegrating action of the part of the body in which it has lodged, or not.

### The Varieties of Cancer.

The varieties of cancerous disease likely to arise in any particular part of the body, are determined mainly by local structural peculiarities, as I have previously mentioned; the history of these, therefore, properly belongs to that of the local forms of cancer.

But all cancers may manifest acute and chronic variations, which are of great clinical importance; and these are the varieties to which I here propose to limit my remarks.

Acute cancers are those in which the average course of the malady, for the special locality, is markedly abridged; while, in chronic cancers, its duration is prolonged far beyond the average.

By way of illustrating the chief features of each of these varieties of cancer, it seems desirable to study specific examples thereof in typical localities, such as the mamma and uterus.

**Mamma.**—Although epithelial cancer of the breast is usually a chronic disease—the average duration of life according to my calculation [1] being from four to five years—yet certain cases occasionally run a very *acute* course. Of these the following types may be recognized:

1. A very rare diffuse form—denominated by the French *cancer d'emblée, squirrhe ligneux en masse* by Velpeau, and *mastitis carcinomatosa* by Klotz—in which the whole of one or both breasts may be at once involved. It arises suddenly, progresses rapidly, and is often accompanied by inflammatory phenomena. No special tumour is formed, but the whole breast becomes enlarged and hard, the skin reddened, œdematous and adherent, and the subcutaneous veins unduly visible. Verneuil and Estlander found the temperature of the affected skin from $\frac{1}{2}°$ to $2°$ above the normal; and the former has demonstrated, in some cases, a veritable cancerous fever.

The adjacent lymph-glands are usually soon invaded, and there is general dissemination of the disease, with death from acute cachexia. Its total duration seldom exceeds a few months; and instances have been reported by Billroth and Aitken, in which it proved fatal within six weeks. Most cases—but not all—arise in connexion with pregnancy or lactation; under these circumstances the disease is apt to be mistaken at first for acute mastitis.

Examples of this type of acute cancer have been reported by Darey,[2] Terrillon,[3] Kautorowicz,[4] Monod,[5] Billroth,[6] Aitken,[7] Volkmann [8] and others.

[1] "Diseases of the Breast," 1894, p. 366.
[2] *Middlesex Hospital Journal*, 1899, vol. iii., No. 1.
[3] *Bull. Gén. de Thérap.*, May 13, 1891, p. 385.
[4] *Cent. f. path. Anat.*, 1893, Bd. iv., S. 1817.
[5] *Gaz. Méd. de Paris*, 1886, pp. 1, 17, 37, and 48.
[6] *Deutsche Chir. Lief.*, xli., S. 128.
[7] *Medical Times and Gazette*, 1857, vol. i., p. 357.
[8] "Über Mastitis carcinomatosa gravidarum et lactantium." Inaug. Diss., Halle, 1869.

2. Although I do not regard the *squirrhe tégumentaire* of Velpeau as a distinct variety, but merely as a peculiar form of subcutaneous dissemination of ordinary acinous cancer, yet it will be convenient to describe it here. Acinous cancers, that originate beneath the nipple and areola, are specially prone to be followed by acute dissemination in the subcutaneous tissue, owing to early implication of the subareolar lymphatic plexus, and rapid diffusion of cancer cells through its communicating cutaneous branches. Lesions thus induced assume the form either of small tubercles (*squirrhe disseminé*, acute miliary carcinosis), of irregularly shaped discs (*en plaques*), or of diffuse infiltrations (*en cuirasse*). Velpeau, who first clearly differentiated these conditions, thought that some cases were from first to last limited entirely to the skin ; but most pathologists are now agreed that the subcutaneous infiltration is invariably secondary to primary disease of the breast. Cases of this type run a rapid course, and are exceedingly malignant.

According to Estlander, the average duration of life seldom exceeds from five to twelve months. This estimate is no doubt true, for those cases in which the skin is implicated at an early stage of the disease ; but I have seen instances, in which this kind of dissemination did not supervene, until several years after the onset of the primary disease in the breast.

Of 170 cases of mammary cancer consecutively under my observation, there were only 2 instances of *squirrhe dessеminé ;* and but 3 of the cuirassed form of the disease. According to Gross, this latter form of the malady is met with once in every 22 cases.

3. Lastly, I have to call attention to certain cases of mammary cancer which—although they in no way differ morphologically from ordinary acinous cancers—nevertheless run a very acute course. I have met with 6 such cases out of 64 consecutive fatal breast cancers. Nunn[1] has also reported a case of this kind.

Mammary cancers that take more than five years to run their entire course, I reckon as of the *chronic* variety. Such cases are much commoner than is generally supposed ; and the majority of them are morphologically indistinguishable from ordinary acinous cancer (scirrhous).

Of 170 women with mammary cancer consecutively under my observation, in no less than 31 (18·2 per cent.) the disease was of the chronic type ; and in 25 the growth was morphologically of the ordinary acinous kind.

The disease in these 25 chronic acinous cancers had already lasted as follows :—5 to 10 years in 14 cases ; 10 to 15 years in 6 cases ; 15 to 20 years in 2 cases ; 20 to 25 years in 1 case ; and over 25 years in 1 case.

Similarly, of 64 consecutive *fatal* cases that had run their natural course, in 17, or 26·5 per cent., the disease had lasted for upwards of five years ; and of these 14 were of the ordinary scirrhous type.

The total duration of life in these 14 chronic scirrhous cases, was as follows :—5 to 10 years in 8 cases, 10 to 15 years in 5 cases ; over 20 years in 1 case.

I have seen cases in which the disease had lasted for 28, 24, and 17

[1] "Cancer of the Breast," 1882, p. 61.

years respectively. Nunn [1] has reported an instance of chronic breast cancer, in which the total duration of the disease had exceeded 30 years; and when last seen the patient was still able to earn her living as a charwoman.

In point of chronicity, it would be difficult to surpass such cases, even among the atrophic and colloid varieties of the disease, which are generally supposed to have a monopoly in this respect.

The *atrophic* form of cancer is certainly rare, for of 170 consecutive mammary cancers, I met with only 6 instances of it, or 3·5 per cent.; but, according to Gross, atrophic varieties constitute 7·9 per cent. of all breast cancers.

The characteristic feature of this type is the continuous, gradual shrinking of the new formation, and the consequent irregular contraction of the breast, which is often thereby diminished rather than increased in size. The deformity produced is apt to resemble that met with in "chronic cirrhosing mastitis." These atrophic, cicatrizing or cirrhosing cancers, usually begin with obscure hardness, which progresses slowly, forming at length ill-defined, flattened or irregularly nodulated thickening, with numerous "roots" stretching far into the adjacent parts. Such growths consist of very dense, whitish, dry, fibroid substance; and, on account of their extreme hardness, they have not inappropriately been designated "stone cancers."

Histologically, the fibrous stroma preponderates, while epithelial elements are very scanty, or altogether wanting. This stroma consists of irregularly disposed bundles of fibrous tissue, rich in elastic fibres, but poor in cellular elements. It contains variously shaped small spaces—atrophied alveoli—in which are a few degenerate epithelial cells, or merely cellular débris and fatty granules. The constituent cells of cancers of this kind are very short-lived, for no sooner have they formed than they thus degenerate; only at their extreme periphery, are proliferous epithelial cells to be found. Usually the disease runs an extremely chronic course, most cases lasting for from ten to fifteen years or more.

Atrophic cancers are specially prone to invade extensively the adjacent tissues by direct extension; and, in a less degree, by local dissemination. Lymph-glandular and general dissemination, although often long delayed, are seldom absent; [2] and recurrence after operation is of frequent occurrence. The secondary growths reproduce the atrophic characteristics of the primary one.

In spite of the chronicity of this form of cancer, it never seems to undergo spontaneous cure.

There can be no doubt that, under the term *colloid cancer*, several different varieties of chronic malignant disease having a gelatiniform aspect, are commonly included. The subject requires to be thoroughly reinvestigated, in the light of modern science. Most of the 75 mammary

[1] Transactions of the Clinical Society, London, 1872, 1878, and 1896.

[2] For a case of twenty-three years' duration, in which there was neither lymph-glandular nor general dissemination, although the opposite breast and adjacent skin, etc., were invaded, *vide* Bontor, Transactions of the Pathological Society, London, 1902.

cases collected by Lange[1] are of ancient date, imperfectly recorded, defective in histological details and in other respects.

The disease is certainly rare, since of 170 consecutive mammary cancers, I have not met with a single instance of it. Lange estimates that only 0·93 per cent. of all breast cancers are of this variety ; and Gross' estimate is 1·34 per cent.

Colloid cancer of the breast, is remarkable for the slowness of its progress.

The disease owes its peculiar features to the proneness of its constituent cells to undergo colloid metamorphosis. In this connexion it must be remembered, that colloid changes normally occur in the secretory cells of the gland, during the early stages of lactation.

Sections of such growths reveal small, translucent masses of glutinous fluid, embedded in the meshes of a fibrous stroma, in place of the usual cellular aggregations. It comparatively seldom happens, however, that the whole neoplasm is thus affected ; for some parts nearly always retain their ordinary scirrhous character.

Histological examination reveals large, thin-walled alveoli, distended with colloid fluid containing granular débris, in which only a few degenerated cells, or perhaps none at all, can be made out. Owing to these changes in the cells, their growth is retarded, and the malignancy of the disease is thereby diminished ; hence colloid cancers run a very chronic course, the average duration of life being about twelve years ; and they are more tardily, and less frequently, followed by local, lymph-glandular and general dissemination, than any other form of mammary cancer. Moreover, in this variety of the disease, cachectic symptoms seldom supervene. When secondary growths do arise, in their main features, they resemble the primary ones.

Colloid cancer usually begins as a small, lumpy swelling in the breast, which increases very slowly. The resulting tumour seldom exceeds the size of a hen's egg, and it may take from ten to fifteen years to attain this size. It generally feels firm and elastic, with projecting bosses. As these growths do not shrink, the nipple and overlying skin are much less frequently retracted than in ordinary scirrhus. Ulceration occasionally ensues at an advanced stage of the disease. Recurrences are less frequent than after the removal of any other form of mammary cancer ; and, when they do occur, they are of tardy development, rarely supervening until from three to ten years after operation.

Many cases of so-called colloid cancer of the breast are really examples of *carcinoma myxomatodes*. In this variety of mammary cancer, the gelatinous transformation is due to myxomatous metaplasia of the fibrous tissue of the stroma ; and, in extreme cases, of its cellular elements as well. Exceptionally, it may even happen that the cancer cells themselves thus degenerate. In this connexion it should be borne in mind, that a layer of mucoid connective tissue is normally present, immediately round the ducts and acini.

A sub-variety occurs—to which the term *cylindroma* has been applied—in which the myxomatous stroma appears as if more or less enclosed in

[1] *Beitr. z. klin. Chir.*, 1896, Bd. xvi., S. 1.

the epithelial ingrowths ; but only a few examples of this kind have been recorded.

**Uterus.**—According to my calculation, glandular cancer of the cervix uteri—the commonest form of uterine malignant disease—runs its course from beginning to end in about two years.[1] Some cases progress more rapidly than others ; but chronic varieties are comparatively rare.

Cases that run their entire course within a year, I reckon as of the *acute* variety. Such cases are by no means rare ; for, of my 90 examples of cervical cancer, 24 were acute, or 26·6 per cent. ; whereas, only 15·6 per cent. of my mammary cancers proved fatal within this brief period. The morphological characteristics of such growths, are usually identical with those of the ordinary cylinder-celled glandular cancer. In some exceptional cases, however, the morbid epithelial elements, instead of assuming the typical tubular form, have been observed to be irregularly diffused in the surrounding stroma, as in certain acute cases of mammary cancer. I have seen it stated, that uterine cancers of this kind are commonest in young women, recently pregnant. My experience gives no support to this statement. In not a single one of my acute cases, did the disease start prior to the age of 30 ; 6 were over 40, 2 over 50, and 1 was 68½ years old at its onset. In none of my cases did the début of the disease coincide with, or occur soon after, parturition.

These facts indicate, that the abnormally rapid progress of the neoplasm depends more upon the intrinsic properties of its constituent cells, than upon extraneous influences. The most rapidly progressive case of my list, ran its entire course in 4·7 months. Kiwisch has reported an instance, in which the total duration was only five weeks ; and Martin's acutest case lasted only nine weeks.

Febrile and pseudo-inflammatory complications may be present ; and widespread generalization of the disease often occurs.

*Chronic* cases, that is to say, cases in which the total duration of the disease exceeds three years, are rarer than acute ones. Of my 90 cervical cancers, 15 or 16·6 per cent., were of this kind. In 3 cases the total duration of life exceeded 7 years. My most chronic case lasted over 7½ years, when the patient, aged 52, died suddenly from the bursting of a pyonephrosis into the peritoneal cavity. The structural characteristics of these chronic growths differed in no respect, from those of the ordinary cylinder-celled glandular cancers. The average age of the patients was 51 years ; that for uterine cancer in general being only 44 years. F. Barker has reported an instance of uterine cancer, in which the disease lasted for 11 years.

Cancer of the corpus progresses less rapidly than cancer of the cervix, the average duration of life, in this form of the disease, being—according to Pichot—about thirty-two months.

Odebrecht has described a case, in which he successfully extirpated the uterus by abdominal section, for a large cancerous tumour of the corpus, that was known to have existed for five years and four months.

Although there is no specific difference between epidermoidal and

[1] For further details, *vide* my book on "Uterine Tumours," 1901, p. 195.

other forms of cancer of the uterus; yet, this form of the disease runs a more chronic course, than is usual with mucosal cancer.

The tendency of these epidermoidal forms is to spread superficially rather than deeply; and the disease progresses towards the vagina, rather than towards the uterus. At a later stage, the pelvic connective tissue is invaded, as well as the bladder, rectum etc. Eventually dissemination in the adjacent pelvic lymph-glands may occur, but metastases are decidedly rare.

Certain epidermoidal-celled cancers of the portio occasionally give rise to chronic, shallow forms of ulceration, that have been described by such names as "corroding ulcer," "ulcus rotundum simplex," "ulcus serpiginosum" etc.

Such ulcers have slightly raised, sharply cut, sinuous edges, with a comparatively smooth base, irregularly studded with small, imperfectly formed granulations, which in places have a florid and almost healthy appearance. A thin, parchment-like layer of cancerous growth generally underlies the affected area, which consists of solid ingrowths of epidermoidal cells, devoid of "nests." In a case of this kind that I investigated, the disease differed in no essential feature from "rodent ulcer."

The term "corroding ulcer" was first applied to chronic ulcerative disease of the os uteri by the brothers Clarke, who first clearly recognized the condition. They thus designated, a slowly spreading, superficial form of intractable ulceration, which gradually involved the whole portio, and eventually destroyed it. The duration of the disease was often ten years or upwards, and the patients affected were generally over forty; thus, in its clinical aspect, it precisely resembles rodent ulcer; but, no anatomical signs of cancer are usually noticeable in connexion with it.

Very few specimens of this rare affection have hitherto been submitted to careful histological examination; in a typical example recorded by J. Williams, no cancer structures were detected.

Too much importance need not be attached to a few negative indications of this kind, since the epithelial elements in rodent ulcer are often scanty, and the small round-celled infiltration very abundant; hence, long after Jacob had differentiated rodent ulcer as a clinical entity, it was nevertheless classed as a non-cancerous disease. Moreover, instances of tuberculous ulceration of the uterus, especially those of the lupoid type, have no doubt often been described as "corroding ulcer." As to whether any form of ulcerative disease, answering to the description of "corroding ulcer," ever occurs in the uterus, as a consequence of local malnutrition dependent upon obliterative arteritis etc.—as Beuttner, John Williams and others maintain—I am certainly sceptical.

## CHAPTER XX

## RECURRENCE

No feature of cancer has attracted more attention than that which is known as "recurrence." It certainly does seem extraordinary, after everything has been done to ensure its destruction—whether by the knife, by fire, or by caustics—that the disease should, nevertheless, so frequently spring up again. As Lebert says, "*Récidive est la règle et presque la loi.*"

Before attempting to explain this remarkable phenomenon, I propose briefly to set forth the chief known facts relating to it.

In the great majority of these cases, the recurrent disease makes its first appearance in the locality occupied by the primary disease, less frequently in the adjacent lymph-glands, and—rarest of all—in remote parts of the body.

There are well-marked differences in respect to recurrence between sarcomatous and epitheliomatous tumours; as a rule, local and lymph-gland recurrence is much less frequent with the former than with the latter type of cancer, while as to metastatic recurrence it is just the converse.

Thus, with regard to malignant epithelial tumours of the *mamma*, Gross' analysis[1] of 543 recurrences shows that about 83 per cent. of them were located in the mammary region (with lymph-gland recurrence as well in 23·5 per cent.); and in the axillary glands alone in 15·5 per cent.

Of 47 recurrent mammary cancers of this kind under my observation, the disease first reappeared in the primarily affected mammary region, in 21 cases; in the mammary region and in the axillary glands, at about the same time, in 18 cases; and in the axilla alone, in 8 cases.

With sarcomata of this part local recurrence is much rarer, since it was met with only in 21·4 per cent. of my cases, in 25 per cent. of Schuoler's, and in 58 per cent. of Gross'; while, with this form of the disease, lymph-gland recurrence is most exceptional.

In 1·61 per cent. of Gross' cases of epithelial cancer of the breast, the disease recurred in the opposite mamma; in 2 of 14 cases of mammary adeno-sarcoma under my observation, there was recrudescence of the disease in the opposite breast, but none at the primary seat.

Reappearance of the disease in parts of the body not directly connected with the primary epithelial cancer or its derivatives (so-called metastatic recurrence), was found by Gross to have taken place in 178 out

[1] "American System of Gynæcology," vol. ii., p. 301.

of 1,030 mammary extirpations, or in 17 per cent.; but, in 129 of these cases, there was local or lymph-gland recurrence as well.

With regard to mammary sarcoma, there is no information available, showing the comparative frequency of metastatic recurrence.

Local recurrences, when first noticed, usually present as small nodules; their initial situation being either in the operation scar, or its immediate vicinity—rarely elsewhere. There has been much discussion, as to whether these recurrent lesions are of more frequent occurrence in the cicatrix of the operation wound, or in its vicinity. It is now generally agreed, that the latter is the seat of their maximum incidence; thus, of Halstead's[1] mammary-cancer extirpations, 16 per cent. recurred in the structures adjacent to the operation scar, as against 6 per cent. in the scar.

Considering the frequency with which radical operations are now being done for *uterine* cancer, it is regrettable that the phenomena of its recurrence, have not yet been studied with that thoroughness which is desirable.

It has, however, been clearly ascertained; that, in the immense majority of cases, the recurrent lesions, which are almost invariably multiple, make their first appearance in the locality of the primary disease, or in the region immediately adjacent thereto.

Most observers are agreed that—after partial hysterectomy—it is in the para-cervical and para-vaginal tissues, adjacent to the extirpated part, rather than in the uterine stump, that recurrent lesions first appear; and, after more radical operations, it is in the adjacent para-metrium that the disease first reappears.

Thus, of 58 recurrences, after the extirpation of cervical cancer, Winter[2] found that 54 were in this locality; and Hofmeier[3] reports that of 47 operated cases—in which recurrence took place during the first year after partial vaginal hysterectomy—the disease reappeared in the adjacent para-metrium in 45 cases.

It appears to be rare for the initial manifestation of recurrence, to originate in the ilio-pelvic or lumbar glands; but I know of no really satisfactory observations bearing directly on this subject. Winter, however, states that he has never observed a case of this kind; and of 44 necropsies—after total extirpation of the cancerous uterus—lymph-gland recurrence was found only in 2 cases.

As to the relative frequency of recurrence in the ovaries, tubes, and adjacent parts of the broad ligaments—when these have been left behind—there is also lack of precise information.

So-called metastatic recurrences are extremely rare; for, Winter met with only 9 instances, after 202 operations.

If we compare with these epithelial cancers, the recurrences of sarcomata of the choroid and femur, marked differences are noticeable.

Thus of 285 intra-ocular sarcomata, for which the diseased eye had been removed, Fuchs[4] found local recurrence in only 31, or in 13 per cent.;

[1] Johns Hopkins Hospital Report, 1894, vol. iv., No. 6.
[2] *Zeits. f. Geb. u. Gyn.*, Bd. xxvii., S. 101; also *ibid.*, 1892, Bd. xxiv., S. 141.
[3] *Ibid.*, Bd. xxxii., S. 97.
[4] "Das Sarcoma des Uvealtractus," Wien, 1882.

and lymph-gland recurrence was hardly ever noted; but, of those who died after the operation, nearly all succumbed to metastatic recurrence.

Similarly, of 103 cases tabulated by Lawford and Collins,[1] local recurrence was noted in only 7 instances, and lymph-gland recurrence not at all; but, 23·9 per cent. of those who had survived extirpation of the eye, were known to have died of metastatic recurrence.

Of 14 recurrences, after amputation for periosteal sarcoma of the femur, tabulated by Butlin,[2] 7 were local, and 7 metastatic.

The *period* at which recurrences first present is exceedingly variable; and the numerical results obtained by different investigators are often divergent.

Of 47 consecutive mammary epithelial cancer cases, under my observation, the average interval between the operation and the first obvious recurrence was 26 months, the maximum 130 months, the minimum a few weeks. These results are more favourable than those arrived at by my predecessors; thus, according to Gross, the average period of immunity only amounts to 9·4 months.

The elaborate analysis by Rieffel,[3] of 687 operated mammary-cancer cases, shows the periods at which recurrences may be expected, as follows:

| Interval between Operation and First Obvious Recurrence. | Total Number of Cases. | Percentage Numbers. |
|---|---|---|
| First to end of fourteenth day | 35 | 5·09 |
| Fifteenth day to end of first month | 91 | 13·24 |
| Second month to end of third month | 181 | 26·34 |
| Fourth month to end of sixth month | 137 | 19·94 |
| Seventh month to end of ninth month | 75 | 10·91 |
| Tenth month to end of twelfth month | 52 | 7·28 |
| Thirteenth month to end of eighteenth month | 54 | 7·83 |
| Nineteenth month to end of twenty-fourth month | 17 | 2·47 |
| Second year to two and a half years | 11 | 1·60 |
| Two and a half years to three years | 10 | 1·45 |
| Three years to four years | 15 | 2·18 |
| Over four years | 9 | 1·31 |
| Totals | 687 | 99·64 |

From this table it will be gathered, that about 64 per cent. of all mammary-cancer recurrences take place within the first six months after operation; and, of these, about 44 per cent. originate within the first three months. Over 18 per cent. occur within the first month, and 5 per cent. within the first fifteen days. The proportion of recurrences attributed by Gross and Winiwarter to the first month, is considerably higher than the above-mentioned figure. Less than 4 per cent. of all recurrences originate after the third year; and, after the fourth year, the number is much smaller. On the other hand, over 82 per cent. of all recurrences originate during the first year after operation.

[1] Royal London Ophthalmic Hospital Reports, December, 1891, vol. xli.
[2] "Operative Surgery of Malignant Disease," 1887, p. 49.
[3] "De quelques points relatifs aux récidives et aux généralisations des cancers du sein chez la femme" (*Thèse de Paris*, 1890).

The following tabular statement, based on 144 cases of cancer of the cervix uteri collected by Hache, shows the periods at which recurrence may be expected after complete vaginal hysterectomy.

| | |
|---|---|
| Under 3 months .. .. .. .. .. | in 19·4 per cent. |
| 3 to 6 months .. .. .. .. .. .. | „ 18·0 „ |
| 6 to 9 months .. .. .. .. .. .. | „ 10·5 „ |
| 9 to 12 months .. .. .. .. .. .. | „ 7·6 „ |
| 12 to 18 months .. .. .. .. .. | „ 12·5 „ |
| 18 to 24 months .. .. .. .. .. | „ 9·8 „ |
| 2 to 3 years .. .. .. .. .. .. | „ 14·6 „ |
| Over 3 years .. .. .. .. .. | „ 7·6 „ |

From this we learn that over 55 per cent. of all recurrences belong to the first year ; and that, nearly 20 per cent. of these originate, during the first three months. On the other hand, only 7·6 per cent. of recurrences appear after the third year.

The incidence of recurrence is much influenced by the stage of the disease at which operative interference is undertaken ; as well as by the more or less thorough nature of the operative procedure adopted ; and probably, to some extent, by the seat of the primary disease.

Thus the liability to local recurrence, after the extirpation of mammary cancer, has been reduced by the earlier and more thorough operative precedures now in vogue, from over 82 per cent., to 50 per cent., and even less ; while, at the same time, the proportion of patients well and free from any return of the disease, for upwards of three years afterwards, has increased from less than 4 per cent., to from 20 to 30 per cent.

Similarly, Leopold found that of 59 early operated cancers of the cervix uteri—in which there were no signs of extension of the disease to the para-metrium—recurrence took place in 14, or in 23·7 per cent. ; whereas, of 68 advanced cases—in which the para-metrium was obviously involved—there was recurrence in 45, or in 66·1 per cent. Krukenberg's data are of similar import. Ott reports that of 8 early vaginal total hysterectomies, 7 patients were still free from any return of the disease, for periods varying from one to over three years after operation, and in only 1 patient had the disease recurred within one year after extirpation ; whereas, after 9 similar late operations, recurrence followed in every case, at periods varying from one to eleven months. These figures show the necessity for early operation.

Another effect of thorough operations has been, to add considerably to the duration of the life of those who have survived them.

I have tabulated all the fatal cases of breast cancer, that came under my observation at the Middlesex Hospital, during a period of six years, with the result that the average duration of life—dating from the time when the disease was *first noticed*—was 60·8 months for those who underwent operation, and 44·8 months for those in whom the disease ran its natural course. Thus, the average duration of life for the *operated cases*, was 16 months longer than for the non-operated ; and, after extirpation of the primary disease, the former lived—on the average—for 40·3 months, that is to say, nearly as long as the entire duration of the life of the non-operated. Moreover, the number of those who died before the end of the third year after operation was 40 per cent. ; whereas, of the non-operated, the number who died prior to this period was 53 per cent. In cancer of other localities, equally good results have followed bold attempts to completely extirpate the disease.

Second recurrences are fairly common. I have met with them in 8 out of 43 recurrent mammary cases (18·6 per cent.); and Rieffel, in 134 out of 687 such cases (19·5 per cent.). The earliest date at which second recurrences appeared, in the 8 cases under my observation, was a few days after the operation; the latest, 130 months after; and, the average interval, was 23·2 months. In these same 8 cases, the first recurrence appeared on the average 41·5 months after operation. This supports Thiersch's dictum, that the interval between operation and recurrence, tends to shorten with each successive operation.

Third recurrences are rare: there was only 1 instance of the kind among the 43 recurrent mammary cancers of my list (2·3 per cent.), and 30 among Rieffel's 687 cases (4·3 per cent.).

Fourth recurrences are so highly exceptional, that Rieffel's list of 687 recurrent cases comprises only 7 instances, or rather more than 1 per cent.

Many instances of patients remaining free from return of the disease, after two or more operations for recurrence, have been reported; Plicque has collected the records of 97 cases of this kind. Poulsen has also reported instances in which, during the first year or two after the initial operation, one or more recurrent tumours had been removed; yet, the patients were well and free from any return of the disease, from eight to nine years after the last operation. Gouley [1] has met with 2 cases of recurrent breast cancer, under observation twenty and twenty-five years respectively after the first operation, in which the patients were well and free from recurrence when last seen—upwards to five years after the last operation.

I shall subsequently have to refer to other instances of this kind. After excision of epithelioma of the lower lip, recurrent for the third time, J. Hutchinson [2] had the satisfaction to find his patient free from any return of the disease, fifteen years later.

It is in the operative treatment of the less malignant forms of sarcoma, that recurrences are most frequently encountered. In dealing with mammary sarcomata of this kind, as many as 4, 5, 6, 7, 12 operations and upwards for recurrent disease, have often been reported.

In a remarkable case of small spindle-celled sarcoma of the breast, in a single woman aged forty-four, as described by Gross,[3] 22 operations were done and 54 recurrent tumours removed, in the short space of four years. Yet, when last heard of, over ten years after the final operation, this patient was in good health and free from any return of the disease.

Occasionally recurrence sets in *immediately* after operation, as in the following case under my observation:—

A stout, healthy-looking woman, aged sixty-eight, with very large mammæ, had a movable tumour—of three months' growth and the size of a turnip—in the middle of her right breast. There was no obvious

[1] *New York Medical Journal*, 1888, vol. ii., p. 396.
[2] *Archives of Surgery*, April, 1892, p. 339.
[3] "American System of Gynæcology," vol. ii., p. 247.

implication of the axillary lymph-glands. The breast was amputated, without opening the axilla. Immediately afterwards, acute diffuse recurrence set in, which involved the whole wound. The skin, pectoral and intercostal muscles, ribs and pleura, were quickly inflltrated. Six weeks after operation, death ensued from hydrothorax and collapse of the right lung, owing to direct extension of the disease through the chest wall. At the necropsy, the right parietal pleura was found to be studded throughout with cancerous nodules; and it showed signs of recent acute inflammation. The diaphragm and liver contained numerous secondary growths, but none were present in either of the lungs, nor in the left pleura. It was a case of *acute traumatic malignancy*, after operation.

At other times, recurrence is delayed for many years—even for from twenty to thirty years; thus, of 250 mammary-cancer patients operated on by Velpeau,[1] 20 remained free from recurrence for periods of from five to twenty-seven years, or 1 in $12\frac{1}{2}$. Nunn[2] and others have had similar results. Of the 47 recurrent mammary cases in my list, there are, however, only 2 instances, in which the period of immunity extended to ten years.

A striking example of tardy recurrence is afforded by members of the family, whose history Sibley[3] has recorded, in which the mother and her five daughters all had cancer of the left breast. Two of these sisters passed eleven and twelve years respectively, after removal of the primary disease, without recurrence; and, upon its return at those dates and repetition of the operation, each remained free from its return for seven years more, and they were still free when last heard of.

The two following cases of late recurrence have come under my own observation:—

*Case* 1.—An emaciated woman, aged sixty-two, with a large, hard mass of ulcerated recurrent cancer in the right mammary region, and cancerous glands in the axilla and lower part of the neck. About twelve years previously she first noticed a lump in her right breast, which was amputated soon afterwards. Ten years afterwards, several small recurrent nodules appeared in the vicinity of the scar and in the axilla; which were soon afterwards excised. Six months later the present recurrence set in. No further operation was done. She died of pulmonary complications, apparently due to invasion of the chest by the local disease, some two and a half months later.

*Case* 2.—A well-nourished, healthy-looking woman, aged fifty-eight, with a nodule of atrophic recurrent cancer—the size of a hazel-nut—at about the middle of the old scar in the left mammary region; and no obvious enlargement of the axillary glands. Twenty years previously she first noticed a small, hard lump, in the middle of her left breast. It slowly increased. Ten years later the breast was amputated. She remained quite free from any return of the disease until six months ago, when the present recurrence was first noticed. It was excised, and the wound had healed a fortnight later.

1 "Traité des Maladies du Sein," Paris, 1854.
2 "Cancer of the Breast," 1882, p. 45.
3 Medico-Chirurgical Society's Transactions, vol. xlii., p. 111.

The longest period of immunity known to me, is in cases reported by Heurtaux [1] and Verneuil,[2] in each of which the disease recurred *in situ*, thirty years after extirpation of the breast for the primary cancer. Bryant [3] has seen similar recurrence, in the same local form of the malady, after twenty-five years immunity ; and Nunn [4] after sixteen years.

Péan [5] has seen local recurrence set in, twenty-five years after amputation of the breast, for primary adeno-cystic sarcoma.

Bucher [6] reports recrudescence of cancer in the opposite breast, six years after extirpation of its fellow for the primary disease, without recurrence *in situ.*

I have previously referred to Schmidt's case,[7] in which, seven years after extirpation of the breast for primary cancer, without local recurrence, there was return of the disease in the liver and lungs.

Such cases illustrate the extraordinary differences that obtain in relative malignancy, between cancers of the same variety—morphologically indistinguishable—in the same locality, and apparently under similar conditions.

With cancer of the cervix uteri, very late recurrences are of much more exceptional occurrence, than very early ones.

Pamard [8] has reported a case of the recurrence of cervical cancer, fifteen years after the extirpation of the primary disease by supra-vaginal amputation, with the galvano-caustic wire-snare. The diagnosis was histologically verified.

Fraenkel [9] has seen recurrence, eight years after removal of the primary disease, which was squamous epithelial cancer of the portio.

It is most exceptional for recurrence to supervene, after total hysterectomy, at a later period than 4 years subsequently to the operation ; but, Leopold reports having met with recurrence first appearing at 8, 7, $6\frac{1}{2}$, and $5\frac{3}{4}$ years respectively, after hysterectomy.

In cancer of other parts of the body, similar instances of tardy recurrence may also be met with.

Guinard [10] has seen lingual cancer recur, in the adjacent part of the right half of the tongue, $18\frac{1}{2}$ years after extirpation of the left half, for primary epithelioma, without any return of the disease in the interval ; and of Kocher's [11] reported "cures," after extirpation of the tongue for the primary disease, in two the malady is known to have returned *in situ*, 10 and 12 years respectively afterwards ; and, in one other "cured" case, the patient died 7 years after extirpation, of cancer of the stomach.

In 2 of 15 cases of recurrent cancer of the lower lip under my observation, there was recrudescence of the disease $6\frac{1}{2}$ and $8\frac{1}{2}$ years respectively, after the primary extirpation : in the former of these cases, the operation scar at the middle of the lip was quite healthy-looking, the recurrent cancer being distinct from it—at the outer part of the left half of the lower lip ;

1 *Arch. Prov. de Chir.*, 1899, No. 2.
2 *La Semaine Méd.*, 1888, p. 112.
3 "Diseases of the Breast," 1887, p. 158.
4 *Op. cit.*
5 *Leçons de Clin. Chir.*, 1892, p. 960.
6 *Ziegler's Beitr. z. path. Anat.*, etc., 1893, Bd. xiv., S. 94.
7 *Beitr. z. klin. Chir.*, Bd. iv., Heft 1.
8 *La Gynécologie*, February 15, 1899.
9 *Cent. f. Gyn.*, 1890, Bd. xiv., S. 891.
10 *Bull. et Mém. de la Soc. de Chir. de Paris*, 1903, No. 14.
11 "Text-book of Operative Surgery," 1895.

in the latter of these cases, the operation scar was also quite sound, the disease having reappeared in the glands of the neck.

Thirteen and a half years after extirpation of buccal epithelioma, Haberer [1] found recurrence *in situ*, the patient having remained well and free from return of the disease, in the interval.

An interesting case has been recorded by Fisher and Box [2] of a man, whose eye having been extirpated for a malignant, pigmented, intra-ocular tumour of the ciliary region, 14 years later died of a large, pigmented, malignant tumour of the liver, similar in structure to the primary intra-ocular tumour, of which there had been no local return.

In the preceding chapter I instanced a similar case by Hulke, in which the period of immunity was over 10 years.

English [3] has also reported an instance of death from recurrence in the liver, 21½ years after extirpation of the primary disease—cancer of the rectum—without any other recrudescence of the malady.

These examples of tardy recrudescence of the disease show, that it is impossible to fix on any arbitrary time limit, beyond which there is no risk of recurrence.

As mentioned in the opening chapter of this work, recurrence *per se* cannot be regarded as pathognomonic of malignancy. It accords with this, that some of the most inveterate and striking instances of recurrence are met with among tumours, not otherwise remarkable for their malignancy, such as rodent ulcer, spindle-celled and myeloid sarcoma, keloid etc. Moreover, non-malignant tumours sometimes form again after removal, in the same locality ; and occasionally these recurrent tumours manifest malignant properties, notwithstanding the benignancy of the primary tumour, of which many instances have been met with after the removal of non-malignant ovarian cystoma etc.

Some non-malignant tumours, such as subungual exostosis of the great toe,[4] condylomata, warts etc., commonly recur after removal, unless the tumour matrix is thoroughly extirpated.

Even with such affections as macrodactyly, the giant growth has been known to recur in the previously normal stump, after amputation of the affected part together with its phalanges, of which Settegart [5] has reported an interesting example ; and Sato [6] has seen recurrence, after the extirpation of a redundant mammary structure.

### Recurrence of Ovarian Cystoma.

Here it seems desirable briefly to consider the chief facts as to recurrence, after the removal of non-malignant tumours, especially ovarian cystoma, as such knowledge throws light on some of the obscure problems relating to the recurrence of malignant tumours ; and, the time has

[1] *Wien. klin. Woch.*, 1902, No. 35.
[2] *British Medical Journal*, 1900, vol. i., p. 639.
[3] *Lancet*, 1904, vol. ii., p. 596.
[4] *Vide* an essay by the author on "Subungual Exostosis," *Bristol Medico-Chirurgical Journal*, March, 1904, p. 17.
[5] *Berlin. klin. Woch.*, November 9, 1906, S. 1007.
[6] *Lancet*, 1907, vol. ii., p. 753.

come, when it ought to be rescued from the obscurity of the dispersive specialities.

After the removal of one or both ovaries by laparotomy for non-malignant cystoma, recurrence occasionally ensues in the form of cystic disease like the original; but sometimes, under similar circumstances, a cancerous form of recurrence supervenes.

Ovariotomy statistics show that non-malignant recurrences are met with, in from 2·5 to 3·5 per cent. of all operations for benign cystoma. The usual seat of these secondary tumours is, in the vicinity of the original cystoma; but, they may be found in any part of the track of the operation wound. Such tumours generally arise from remnants of the original tumour left behind at the primary operation, or from fragments detached and implanted in the wound or its vicinity; and, in the event of antecedent rupture of the cystoma, detached secondary tumours may be found at the time of the initial operation.

After the removal of a unilateral cystoma without interference with the opposite sound ovary, fresh cystic disease may develop in the latter, as many reported cases testify. Cystic disease of a sound ovary, left behind after removal of the myomatous uterus together with a diseased ovary, has also been noted, as in a case lately reported by Calmann.

Even bits of normal ovarian tissue, such as are sometimes left behind after oöphorectomy, may subsequently originate cystic tumours, of which examples have been recorded by Martin, Pozzi, P. Müller and others.

Here it may be remarked, that recurrent tumours of the kind we are now considering, have been known to form even after the most radical operations, involving extirpation *en masse* of the ovaries, uterus and adnexa; when it is highly improbable that any fragments of the ovaries—normal or cystic—could possibly have been left behind.

Even if the presence of aberrant accessory ovarian structures in the pelvic region and its vicinity, had never been actually demonstrated, I maintain that it would nevertheless be possible, for one thoroughly acquainted with the ensemble of the facts relating to conditions of this kind, to predicate that such aberrant structures do exist. But accessory, detached, ovarian structures have many times been detected, not only in the immediate vicinity of the ovary; but also in the broad ligaments, and in more remote localities—intra- and extra-peritoneal. To this source may be ascribed many of the recorded cases of ovarian-like cystomata, arising primarily in para-uterine, para-vaginal and para-vesical regions, in the round ligaments, and even in the lower part of the abdomen, quite outside the peritoneum (Fergusson, Meredith, Olshausen, Kaltenbach, Winternitz, and others). Moreover, dermoid and Wolffian structures have been found associated with these tumours, as with their ovarian congeners.

It quite accords with this explanation, that menstruation is fairly often re-established after double oöphorectomy for various morbid conditions of non-ovarian origin, as well as after double ovariotomy for cystoma; and pregnancy has often been known to ensue, after both of these types of operation.

It is to aberrant accessory ovarian structures of this kind, that we must look for the origin of many of these recurrent ovarian cystomata.

Velitz[1] has collected and analysed 135 cases of recurrent ovarian cystoma; in 56 of these, the second operation was for the removal of cystic disease which had supervened in the ovary left behind at the first operation; and, in 14 other cases, for recurrent disease otherwise arising. In 8 cases, a third operation was necessary; and in 1, five operations were required.

The period at which these benign recrudescences of cystoma first attract notice, varies from 1 year to over 20 years, after the initial operation; but, a relatively large proportion of them are of tardy development, that is to say, they are not noticed until from 5 to 10 years or more after operation.

It follows from what has been stated, that the germs of these recurrent cystomata are either detached fragments of the original tumour; or ovarian tissue, left behind at the initial operation—in the form either of an unextirpated entire ovary, of detached fragments of a normal ovary, or of accessory ovarian structures, subsisting in the vicinity of the ovary, or at some distance from it.

In this connexion we must also bear in mind, that polycystic quasi-ovarian tumours may possibly arise from adrenal "rests" in the vicinity of the ovary, according to Pick and Eastwood; although, it seems to me, that the adrenal origin of neither of their tumours has been clearly proved.

In very exceptional instances, similar forms of local recrudescence are met with, after the removal of uterine myoma,[2] mammary fibro-adenoma; and other non-malignant tumours.

We are now in a position to examine the numerous cases recorded of late, in which the removal of a non-malignant ovarian cystoma has been followed by the outbreak of cancer.

These cases may be divided into three categories.

In the first may be placed those rather numerous instances, in which it seems obvious that the cancerous disease has originated from detached fragments of the original cystoma, implanted in the track of the operation wound or its vicinity, or left behind *in situ*. Growths of this kind have been met with in the cicatrix of the abdominal wall; in the site of the removed cystoma, its pedicle, or adjacent structures; and diffused throughout the peritoneal cavity. Most cases of this kind, develop within a few years after the original operation. In these cases, it seems as if proliferous cells detached from the non-malignant cystoma, subsequently acquired malignant properties, owing to their altered conditions of existence.

In the second class, are those cases in which, after the removal of non-malignant unilateral cystoma, cancer supervenes in the sound ovary, of which I know of several instances; in like manner, as many cases indicate, cancer may arise from accessory ovarian structures, left behind at the first operation.

[1] *Zeitschr. f. Geb. u. Gyn.*, Bd. xx., Heft 2.

[2] Recent cases by Dürch (*Münch. med. Woch.*, 1907, No. 22, S. 1154), Flaischlen (*Zeits. f. Geb. u. Gyn.*, 1904, Bd. li., Heft 3), and in my book on "Uterine Tumours," 1901, p. 88.

The third class comprises a large number of cases in which, after the extirpation of one or both ovaries for cystoma, cancer subsequently supervened in some other part of the body.

Thus, R. Morison has related two instances of mammary cancer supervening in patients, who had undergone double ovariotomy for cystoma: in Poupinel's case, mammary cancer supervened after unilateral ovariotomy, and Pfannenstiel has reported a similar instance.

Butler-Smythe has seen cancer of the cervix uteri develop in a patient, who had undergone double ovariotomy for cystomata, many years previously; and Morestin the same disease, after unilateral ovariotomy for cystoma.

Similarly, many instances have been reported of cancer of the stomach and intestines, supervening after ovariotomy for cystomata.

In his work on "Ovarian Tumours," Spencer Wells gives a table, showing the subsequent history of all those who recovered after completed ovariotomy, for cystoma. It was found that 117 had since died, the causes of death being unknown in 29. Of the remaining 88, no fewer than 32 had succumbed to cancer, that is to say, 1 in 2·75. During the same period, the cancer mortality in the general population, among women of about the same age, was 1 in 15.

Thus, the cancer mortality was nearly five and a half times greater for those, one or both of whose ovaries had been extirpated; than for those who had undergone no such operation.

Of these 32 cancer cases, in 19 the seat of the disease is not stated, in 3 it was peritoneal, in 3 uterine, in 2 in the pedicle, in 2 rectal; and in the lung, liver and kidney, each in 1 case.

The date after ovariotomy, at which death from cancer supervened, is stated in 29 cases; 10 died in the first year, 10 in the second, 4 in the third, and 5 at later periods.

In none of the foregoing cases was there any reason to suspect, at the time of ovariotomy, that malignant disease was then present.

In 6 of the 32 operations, it is distinctly stated that both ovaries were removed.

I have purposely omitted from this estimate four cases, in which malignant disease supervened at very brief intervals after the operation; but, these may well have been instances of acute traumatic malignancy caused by the operation, such as we occasionally see in other parts of the body, after operative procedures for the removal of non-malignant tumours.

In short, the cumulative evidence of modern experience shows, that the supervention of malignant disease is of exceptional frequency, after operations of this kind; and Kratzenstein[1] has collected a hundred examples of it, without having exhausted the records.

Some authors have endeavoured to account for the frequency of cancer after ovariotomy for cystoma, by alleging that these cystomata are really often malignant tumours. Such an opinion is, I believe, erroneous, for the following reasons:—(1) It is in direct conflict with the mortality statistics of this country, and of all countries where reliable

[1] *Zeitschr. f. Geb. u. Gyn.*, Bd. xxxvi., S. 61.

records are kept, which show that primary malignant disease of the ovaries is decidedly rare—much rarer than it would be if this explanation were correct; [1] (2) the information furnished by the statistical records of large hospitals, where cases of this kind are carefully scrutinized, and where a considerable proportion are submitted to post-mortem examination, is entirely in accord with that derived from the national statistics; (3) moreover, during ovariotomy and at the examination of the tumour after its removal, no signs of malignancy could be detected in any of the cases included in Spencer Wells' list.

If further evidence as to the correctness of my views on this matter is required, plenty is forthcoming.

Ovariotomy for cystoma, is not the only abdominal operation after which malignant disease often develops. A very large number of cases have now been recorded, showing the frequency of the supervention of malignant disease after removal of functional ovaries, for various morbid conditions.

Thus, after amputation of the uterus, together with the ovaries and adnexa, for myoma of the uterus, many instances of the subsequent supervention of cancer have been reported, *e.g.*, 18 by Schenk, 11 by Schauta, 8 by Sänger, 5 by Savor, and a great many by other authors.

Similarly, after double castration for various morbid (non-ovarian) conditions, cancer has often been known to eventuate, *e.g.*, cancer of the uterus, two years after the removal of both ovaries and tubes for pyosalpinx (Playfair); uterine cancer eight years after double oöphorectomy for myomata (Blacker); sarcoma of uterus, many years after removal of both ovaries for myomata (H. Spencer); cancer of cervix of uterus, three years after removal of both ovaries for dysmenorrhœa (Herman) etc.

From the foregoing considerations it follows, that damage to the ovaries by disease, or their removal by operation, greatly increases the proclivity to cancer.

Of like import is the series of cases reported by Neugebauer,[2] illustrating the proneness to malignant and other tumours, of persons with rudimentary, badly developed or absent ovaries—to which list many cases have since been added.

The great frequency of cancer in castrated animals, to which I have previously referred, also points in the same direction.

Thus, then, may we explain the special proclivity to cancer, manifested by patients who have undergone ovariotomy for non-malignant cystoma.

### Rationale of Recurrence.

Returning now from this digression to our rationale of recurrence, careful examination of recurrent malignant growths has revealed the important fact, that in their morphological and other characters, they closely resemble the primary neoplasm. From this we may infer, that

[1] For the precise figures, *vide* Chapter XII.
[2] *Cent. f. Gyn.*, 1890, No. 18, p. 1.

they originate from the latter or its derivatives ; or that both spring from a similar matrix. These are, in fact, the sole sources of recurrent growths.

Here reference may be made to the fact that recurrent growths, like metastases, do sometimes differ somewhat from their primaries : thus Heinbaum [1] has described an instance of melano-sarcoma of the corneo-scleral junction, which recurred *in situ* after local excision, as leuco-sarcoma ; while, in a case of leuco-sarcoma of the sclerotic, treated in the same manner, with freedom from return of the disease for seven years, the malady then recurred in its former site, as melano-sarcoma.

Very significant is it, that the great majority of recurrences are situated either in, or in the immediate vicinity of, the operation wound. In the case of mammary cancer, the researches of Volkmann, Heidenhain, and others, have conclusively demonstrated, that fragments of the original disease are almost invariably left behind after operations undertaken for its removal, as hitherto usually practised.

After the removal of uterine cancer, even by total hysterectomy, Leopold, Mackenrodt, and others, have shown that unextirpated fragments of the disease are frequently left behind.

It seems certain that morbid fragments of this kind, persisting after operation, are the germs whence most recurrent growths originate. Thus may be explained the *initial multiplicity* of most recurrences, wherein they differ so markedly from independent spontaneous outgrowths, which are almost invariably solitary.

The great frequency of recurrence soon after operations, points in the same direction. Hence we may conclude, that the immense majority of local recurrences are due to incomplete ablation of the primary growth. In these cases, there is, indeed, no real reproduction of the disease ; but merely continuation of it, in the surviving unextirpated fragments (*continuation recurrence*).

Similarly, when—after operation—the disease recurs in adjacent lymph-glands, or in remote parts of the body—apparently unaffected before—we may infer that its recrudescence in these situations is generally due to the dissemination there of *seminium* of the primary disease, prior to the operation for its removal, which have subsequently developed, as in the formation of other disseminative growths.

It seems not improbable that some of these local recurrences are due to inoculation of the operation wound with cancer elements, detached by the surgeon's knife etc. To avoid this, Donitz, Sabatier and others, recommend that care should be taken not to cut into such neoplasms during their removal.

There yet remain for consideration those instances of *late* recurrence, appearing several years after operation—of which I have previously described several instances—which cannot be explained in this way, without resorting to the gratuitous assumption, that cancer elements may lie dormant in the tissues for several years, and then suddenly recover their morbid activity. Such cases—which are rare—are, I think, undoubtedly due to independent outbreaks of the disease (*repullulation*),

[1] *Arch. f. Augenheilk.*, Bd. xxxvii., Heft 1.

in unextirpated remains of the structures of the part in which the disease originated.

This explains the usual localization of late recurrences in the primarily affected region, rather than elsewhere; and their more frequent appearance in the vicinity of the operation wound, rather than in the cicatrix.

I have elsewhere [1] directed special attention to the occurrence in the mammary region, its vicinity and the axilla, of detached fragments of redundant mammary glandular structures, whence various malignant and benign tumours may arise.

I have also reported several instances of late recurrent cancer, arising from these aberrant structures; and no doubt a certain proportion of late recurrences, after radical thorough operations, habitually originate thus.

Similarly we may ascribe the origin of certain late recurrences, which occasionally form after abdominal total extirpation of the cancerous uterus—when it is hardly conceivable that any unextirpated remains of the uterine mucosa or its glands could possibly have been left behind—to aberrant "rests" of Wolffian or Müllerian structures, which—as recent researches have shown—abound in the para-uterine tissues and their vicinity.

There still remain, however, certain exceptional instances of late recurrence at a distance, which are not satisfactorily explained by the foregoing hypothesis; such, for instance, as Fisher and Box's case, in which a pigmented intra-ocular cancer reappeared in the liver, fourteen years after extirpation of the eye for the primary disease etc.

In such cases it seems probable that *seminium*, derived from hyperplastic, pre-cancerous elements of the original tumour-matrix, and transported to the liver etc., have subsequently acquired in their new *habitat* cancerous properties. In like manner, cancer is sometimes seen to arise primarily in the glands of the groin, in association with pre-cancerous lesions of the penis and scrotum, as I have previously mentioned. The origin of cancer from non-malignant elements, detached and implanted in the track of wounds made for the removal of ovarian cystoma, uterine myoma etc., long after recovery from the completed operation, are phenomena of similar import.

I certainly think this explanation is more in accord with the known facts, than the alternative hypothesis of latent cancer germs, which has no definitely ascertained facts to rest on.

In a general way, it is to the processes of regeneration and repair, that we must look for the physiological prototypes of recurrence; just as *Hydra* regenerates itself after mutilation, and after it has been cut into small pieces, so it is with these malignant tumours.

[1] "Diseases of the Breast," 1894.

## CHAPTER XXI

## CACHEXIA

After a cancerous growth has existed for a variable time, which is generally rather long, the patient's health begins to suffer—even in the absence of ulceration, hæmorrhage etc. Pallor, weakness, emaciation and loss of appetite, are among the most obvious manifestations. These, as the disease progresses, become greatly aggravated—the pallor taking on a peculiar earthy, or straw-coloured tint—while other indications of profound disturbance of the general nutrition arise; which, when the malady runs its natural course, eventually determine death from asthenia.

The condition thus briefly sketched, is that generally known as the cancerous cachexia; which, as I shall proceed to show, depends upon the entry into the circulation, of products resulting from the disintegration of the constituent cells of the cancerous tumours.

Cachexia is more frequently seen with malignant epithelial tumours, than with sarcomata; and in some varieties of both types of malignant disease—such as rodent ulcer, spindle-celled and myeloid sarcoma—it seldom occurs. Even among the different varieties of the same type of malignant disease, there are great divergencies as to the occurrence of cachexia; thus, it is much more frequently met with in association with cancers, whose constituent cells are specially prone to degenerative disintegration—such as the ordinary acinous cancer of the breast—than with those whose cellular elements are more stable—such as epidermoidal cancer of the lower lip. Yet some destructive metamorphoses of cancer cells, such as the colloid, are not attended with cachexia; as is specially seen in the mammary form of this disease.

Moreover, cachectic symptoms are sometimes induced by very large, non-malignant tumours, especially those of ovarian and uterine origin; and even by such quasi-malignant pseudo-plasms as *mycosis fungoides*.

Similarly, in the constitutional changes coincident with pregnancy and *post-partum* conditions, we see manifested physiological counterparts of cachexia. Hence, there is nothing specific of cancer about it.

The condition certainly cannot be attributed to the mere abstraction of nutritive materials from the blood, as some have suggested; for, it is often met with in its most marked form, in association with quite small cancerous tumours. Neither can it be ascribed to septicæmia; for, it appears to be quite independent of such external lesions, as usually accompany the ordinary septic infections *ab extra;* moreover, there is usually no pyrexia, but the temperature tends rather to be subnormal; and, after death, none of the usual signs of septicæmia are noticeable.

It is noteworthy that cachectic symptoms never precede the outbreak of the primary disease; from this we may infer, that they are a consequence of its local progress. Certain it is, that after removal of the disease by operation, the cachectic symptoms usually disappear; and, in the absence of recurrence, patients may retain their healthy appearance for several years, as in cases I have observed. The degree of cachexia is, however, by no means always proportionate to the mere extent of the local malady; for, I have seen well-marked cachectic symptoms supervene acutely, at an early stage, when the primary disease has been quite small. Neither can it be maintained, that cachexia is dependent upon dissemination; for, it may be absent, when the latter is very marked, and *vice versâ*. Just so it is with regard to hæmorrhage, which affects only a minority of cancer cases. In certain exceptional instances, the disease may even run its entire course, without ever causing any cachexia, or other very obvious disturbance of the general nutrition, the patients being able to follow their usual avocations almost to the last. Indeed, cancer patients seldom take to bed, until the disease has run more than half its course.

Weakness is a much later symptom of this condition than emaciation; and anæmia generally goes before the latter. The precise date at which cachectic symptoms are most prone to supervene, their sequence and degree of development are, however, so variable; that detailed general statements respecting them cannot usefully be made.

We may, I think, best interpret these symptoms, as the result of a general toxæmia, the explanation of which must be sought in the remarkable proneness of the constituent cells of cancers to undergo degenerative changes, which are often so extreme as to lead to their complete destruction by disintegration. When such excrementitious products find their way—by nutritive absorption or otherwise—into the general circulation, in quantities too great to be quickly eliminated and destroyed, they poison the fluids of the body; and so, by a kind of auto-intoxication, similar to that by which the system is infected from an inflammatory focus, they originate the phenomena of the cancerous cachexia. It seems probable, that the excrementitious products thus derived contain toxic albuminoids, analogous to the virulent substances secreted by microbes. Through these agencies the hæmatopoietic organs—especially the lymphatic apparatus—are injuriously affected. Thus the blood of cancer patients gets profoundly modified, both qualitatively and quantitatively. The red blood-corpuscles show signs of progressive deterioration and destruction, while the white ones become much more numerous.

There is, however, nothing specific about these changes, which are similar to those met with in other anæmic states.

It was long ago shown by Andral[1] and Simon that, in cancer patients, the red corpuscles of the blood are greatly diminished in numbers—even in the absence of ulceration and hæmorrhage—and these results have

[1] "Essai d'Hematol. path.," 1843, p. 175.

been confirmed by recent investigators (Hayem and others). Thus, while the number of red corpuscles in a cubic millimetre of a healthy woman's blood is about 4,500,000, in cancer patients—even during the early stages of the disease — the number present is often less than 3,000,000; and—at subsequent stages—it may descend to 1,000,000, or even lower.

In healthy women, the proportion of reds to whites is about 750 to 1; but in those with cancer the ratio varies from 380—60 to 1.

In pernicious anæmia, the diminution in the number of red corpuscles is much greater than in cancer—viz., to 1,500,000 or even 300,000 per cubic millimetre.

Various alterations in the form of the red corpuscles are also met with in the blood of the cancerous, most of which are indicative of degenerative changes (*e.g.*, microcytes and poikilocytes). Hayem maintains that the pseudo-parasitic bodies found in the blood by several observers, are mostly due to conditions of this kind (fragmentation etc.). Probably the minute, highly refractile, amœboid bodies—found by Kahane in the freshly drawn blood etc. of cancer patients—may also be of this nature; as well as Niessen's mycete, which he regards as specific. To enable us to appreciate the worth of these and other alleged cancer microbes in the blood, we need to be better informed than we are at present, as to the organisms that may be found in the blood in health and disease.

In pernicious anæmia, similar degenerative changes, of an even more marked character, are of common occurrence.

Bord and Kullmann claim to have found a hæmolysin in the blood of cancerous patients, which they think may be utilized for diagnostic purposes.

Nucleated red globules (normoblasts) and megaloblasts, are of rare occurrence in most forms of cancer, but common in pernicious anæmia; on the other hand, blood-plates (hæmatoblasts of Hayem) are fairly numerous in cancer—except in advanced stages of the disease—whereas, in pernicious anæmia, these bodies are greatly reduced in numbers, falling from 300,000 per cubic millimetre—the normal—to less than 25,000.

The poverty of the blood of cancer patients in hæmoglobin, has been demonstrated by Quinquaud[1]: 1,000 grammes of normal blood contain about 125 grammes of this substance; whereas, in cancer cases, the amount often does not exceed 25 grammes. The investigations of Bierfrund and others are to the same effect.

The difference between cancerous and non-cancerous blood in this respect is so marked and constant, that Laker[2] maintains it may be relied on for the purpose of differential diagnosis. Marked diminution of hæmoglobin may be detected, even before any deterioration in the patient's general health is noticeable.

In pernicious anæmia, the hæmoglobin is also diminished; but in a less degree than might be expected, considering the great deglobulization.

[1] "Traité technique de chimie biologique," etc., Paris, 1883.
[2] *Cent. f. d. med. Wissenschaft*, 1887, S. 405.

The immediate effect of injecting physiological or microbic poisons into the circulation is, as Löwit [1] has shown, to cause sudden and rapid decrease in the number of leucocytes in the blood (leucolysis), the vascular intoxication at first causing their destruction. If the animal survive, however, marked regenerative leucocytosis soon sets in, the increase being chiefly of the lymphocytes from the irritated lymphoid tissue.

Leucolysis has never been demonstrated in connexion with the cancerous toxæmia; but, the condition being a fleeting one, may nevertheless occur.

Marked increase in the number of the white corpuscles—leucocytosis—is the rule in advanced cancer; but, in early stages of the disease, this condition is usually lacking—especially in cancer of the stomach. Hayem [2] found the number of leucocytes increased from 6,000 per cubic millimetre—the normal standard—to 17,600, in certain cases of cancer of the stomach; to 11,400 in breast cancer; to 7,800 in uterine cancer; and much higher counts have been met with.

Similar conditions have been demonstrated, in connexion with sarcomatous tumours.

Very remarkable diminution of leucocytosis has been noted, after the extirpation of mammary cancer: in one case the leucocyte-count, which was 21,700 before operation, fell to 6,200 soon afterwards; but, with the advent of recurrence, it steadily rose again. Hayem considers that by enumerating the leucocytes, the on-coming of recurrence can be predicted, before any other physical signs thereof are noticeable.

In cases complicated by metastasis, leucocytosis is almost invariable, especially when the osseous system is affected.

Many of the foregoing changes remind us of the effects produced on the blood, by such drugs as pyradine, which cause destruction of the red globules, with increase of the white ones.

In a general way, leucocytosis is regarded by pathologists, as a reaction of the organism to counteract some injurious toxæmia; but, as to whether the increased production of leucocytes is due to stimulation of those organs which produce them (Virchow and Ehrlich), or to chemiotaxic influence at the site of the lesion (Limbeck and Jakob), is still undecided.

The precise rôle of each of the different varieties of leucocytes, in the leucocytosis of cancer, has not yet been satisfactorily determined. Surgeons have hitherto taken but little interest in such matters; and progress is also impeded by uncertainty, as to the origin and development of leucocytes. According to Ehrlich, leucocytes with granulations originate in bone-marrow, and persist in original type throughout life; while non-granular, large and small lymphocytes, are formed in lymph-glands, and then passed into the circulation. Other pathologists consider that leucocytes are developed from small lymphocytes, in lymph-glands and bone-marrow, by a process of "ripening" in the blood-stream; and the leucocytosis of digestion is regarded as an indication favouring this view. Cabot [3] considers that, in the leucocytosis of cancer, the adult forms are

[1] "Studien z. Physiol. u. Path. des Blutes u. d. Lymphe," Jena, 1892.
[2] "Du Sang," Paris, 1889. [3] "Clinical Examination of the Blood," 1897.

unduly augmented, at the expense of the immature cells. Generally, however, this form of leucocytosis is found to be due to augmentation in the number of lymphocytes, which are believed to be produced in excess by the irritated lymphatic organs; nearly as frequently, however, the polynuclear leucocytes (neutrophile of Ehrlich), which normally comprise from 62 to 70 per cent of all leucocytes, are the ones chiefly augmented. It has been determined by Zappert[1] and others, that the eosinophile corpuscles are decidedly diminished in numbers in cancer patients, probably being attracted from the blood to the seat of disease, where they are retained, as after various experimental traumata; but, with regard to the mono-nuclear basophiles or mast cells, beyond the fact that they are met with in cancer, nothing has yet been definitely ascertained.

Myelocytes, which are not one of the normal constituents of the blood, are found in cancer more frequently than in any other diseases, except pernicious anæmia and leukæmia, although the percentage is usually only small.

In pernicious anæmia there is no leucocytosis; indeed, the leucocytes may be much reduced in numbers, even to 1,500 per cubic millimetre.

The most marked changes in the blood in cancer, are those seen in cases presenting metastasis, with secondary growths in the bones. An instructive example of this kind has been recorded by Kurpjuweit,[2] in which a woman, aged thirty-four, with cancer of the pylorus, and dissemination in the liver, retro-peritoneal glands, and osseous system, was found to have the following blood condition: the reds numbered 1,825,000, and the hæmoglobin amounted to only 25 per cent.; the whites numbered 9,100; comprising 48·4 per cent. of polynuclear leucocytes, 11 per cent. of neutrophile myelocytes, 6·6 per cent. of transitional forms between the foregoing, 12·2 per cent. of large lymphocytes, 19·2 per cent. of small lymphocytes, 1·6 per cent. of eosinophile cells, and 1 mast cell in 2 preparations. Here, the myelocytosis pointed conclusively, to implication of the bone-marrow. There was also myeloid metaplasia of the liver, spleen, lymph-glands and medulla of the bones, indicating the abnormal activity of these structures in regenerating the deficient blood elements. Kurpjuweit has collected 13 cases of this kind, in all of which marked anæmia and myelocytosis were associated with metastases in the osseous system. It is this type of malignant disease, which occasionally gives rise to all — or nearly all — of the symptoms of pernicious anæmia, and even of myelogenous leukæmia.

Sarcomatous, as compared with malignant epithelial tumours, seem generally to produce the more profound blood alterations; they are attended with greater anæmia, more pronounced reduction of the hæmoglobin, and a higher degree of leucocytosis, than is usual with epitheliomata.

In making use of leucocytosis for diagnostic purposes, it must be borne in mind that, even in health, the number of leucocytes presents considerable variations. Thus, after a meal, it is greatly increased;

[1] *Zeitschr. f. klin. Med.*, Bd. xxiii., S. 227.
[2] *Deutsche Arch. f. klin. Med.*, 1903, Bd. lxxvii., Heft 5 and 6.

and there is a post-hæmorrhagic leucocytosis, as well as a leucocytosis of pregnancy, of the newly born, and of the dying. Moreover, similar conditions accompany inflammatory and febrile affections.

Persistent leucocytosis with a tumour, unattended by inflammation or suppuration, is generally due to malignant disease.

It has been pointed out by Schneyer[1] and Hartung,[2] and confirmed by others, that the leucocytosis of digestion does not occur in patients with cancer of the stomach; whereas, it is very noticeable in gastric ulcer, pyloric stenosis, and most other non-cancerous conditions. This may aid in distinguishing the latter affections from cancer; but it must not be too implicitly relied on.

Probably no disease can be definitely diagnosed, on the evidence of an examination of the formed elements of the blood alone; and, on the whole, the morphological peculiarities of these elements, generally furnish the most reliable indications.

So far as present experience goes, the serum of cancer patients has been found to yield no agglutin reaction; nor has any specific opsonin been detected in it.

The quantity of albumin and inorganic salts dissolved in the plasma is less than the normal, according to Moraczewski[3]; the phosphorus is notably diminished, as in all anæmias, while there is relative increase of the chlorides. Its alkalinity is also increased; and this is believed to be the cause of the absence of free hydrochloric acid from the stomach in gastric cancer. Even under normal conditions, the body fluids are believed to acquire increased alkalinity with advancing age.

Here it may be noted that there is diminution in the gastric hydrochloric acid, not only in cancer of the stomach, but also in almost all cases of cancer, as well as in various other obscure cachexias.[4]

It is owing to the poverty of the blood in these and other respects—especially to the diminution of its hæmoglobin—that its low specific gravity (1012 to 1016 in some cases of gastric cancer) is due.

On the other hand, an excess of sugar-forming matters is, according to Freund,[5] of constant occurrence.

Such states of the blood explain the tendency in advanced cachexia, to passive serous effusions (hydrothorax, anasarca etc.); as well as to thrombosis (*e.g.*, of the pulmonary artery, iliac veins etc.), to phlebitis, to subacute congestions and inflammatory affections of the lungs, to petechiæ, purpura, retinal hæmorrhage etc. It is specially in cases with metastases in the bones, such as Kurpjuweit has described; and also in cases of general sarcomatosis, such as Martin,[6] Hamilton and Fagge have reported, that lesions of this type are apt to occur.

This deteriorated condition of the blood also enables us to understand, how it is that great losses of this fluid are repaired so much more slowly in the cancerous than in the non-cancerous, to which Bierfrund has called special attention.

Not only are the morphological and chemical constituents of the

[1] *Münch. med. Woch.*, 1894, S. 917.
[2] *Wien. med. Woch.*, 1895, S. 697.
[3] *Arch. f. path. Anat.*, Bd. cxxxix..., S. 385.
[4] B. Moore, *Pro. Roy. Soc.*, March, 1905.
[5] *Wien. med. Blätter.* 1885, No. 9.
[6] *Journal of Experimental Medicine*, 1896, vol. i., p. 595.

blood thus altered; but, as the experiments of Louis[1] show, its total quantity is notably diminished. Thus may be explained the smallness of the heart, aorta, and arterial trunks, in most post-mortem cancer cases, that have run their natural course; although, as Beneke has shown, prior to the outbreak of the disease, cancer patients have large hearts and bloodvessels: and the natural tendency is for the heart and large arteries to increase in size and weight from childhood to old age, as I have mentioned in a previous chapter.[2] It quite accords with these conditions of the circulatory apparatus, that the cancerous cachexia is often associated with vascular hypotension, as Janeway[3] has lately indicated.

One of the most obvious manifestations of this depraved state of the blood, is *pallor* of the skin; which, as the disease progresses, often assumes a waxy, puffy, aspect, together with the peculiar straw-coloured tint so characteristic of the cancerous cachexia. There is, however, nothing specific about it; for a similar condition is met with in other anæmic states, especially in chlorosis and in pernicious anæmia. It is probably due to altered hæmoglobin, taken up by the plasma of the blood.

A later developed manifestation is *emaciation;* which when it has once set in, is steadily progressive, so that the wasting is often extreme. This, like most of the other individual symptoms of the cancerous cachexia, may, however, occasionally be absent.

As the disease progresses *weakness* appears, and increases *pari passu.* *Gastro-intestinal* disturbance is commonly experienced. Loss of appetite, dyspepsia, anorexia, together with thirst, are often prominent symptoms. Nausea and vomiting are also of frequent occurrence, even in the absence of visceral dissemination; and slight jaundice is not uncommon. Constipation oftener exists than diarrhœa; and aversion to nitrogenous food is frequently met with.

It has lately been suggested by Copeman, that many of these symptoms are consequent on the chyme, which enters the duodenum from the stomach after a meal, being insufficiently acid to stimulate an adequate amount of pancreatic secretion.

*Quasi-rheumatic pains* in various parts of the body, remote from the primary seat of disease, such as the loins, hips, lower limbs etc., are often complained of. When these coincide with subacute febrile disturbance, as occasionally happens, the condition may easily be mistaken for subacute rheumatism, of which I have seen several instances. Often pains of a neuralgic character are experienced; as well as numbness and tingling of the hands and feet; and an undue impressionability to cold may be noticeable.

Those who have examined cancer patients for *peripheral neuritis* have often found it—*e.g.*, Isch-Wall,[4] Auche,[5] Gombault, Klippel etc.

Various symptoms also arise owing to disturbance of the sympathetic nervous system; among these I have frequently observed alternate flushing and pallor of the face and hands—sometimes so marked as to

[1] "Researches on Phthisis" (Walshe's translation), 1846, p. 52.
[2] Chapter XVI. [3] "Blood Pressure," 1904, p. 237.
[4] "Cancer et Arthritisme," *Thèse de Paris*, 1890, No. 147.
[5] "Des névrites péripheriques chez les cancéreuses," *Rev. de Méd.*, 1890, p. 785.

suggest Raynaud's disease—cardiac palpitation, syncope, tachycardia, shortness of breath and gastric disturbance. I can also testify as to the correctness of Bogdan's [1] observation; that red patches are frequently visible on the cheeks, owing to dilatation of the superficial bloodvessels. These vaso-motor disturbances are most marked in intra-abdominal cancers (*e.g.*, of the stomach and uterus). Other observers (Cuffer, Riehl etc.) have described various visceral vaso-motor disturbances, which they attribute to inflammation of the sympathetic nerves. Herpetic and erythematous eruptions are also occasionally seen.

In the course of the disease, cancer patients are apt to become irritable and depressed; but I have not noticed any special tendency to moroseness, on which Lebert insists. Headache and insomnia are of frequent occurrence; but the mind usually remains clear to the last.

In a few cases, after the disease has existed for a considerable time, cancer patients become *insane;* the form of mental derangement I have most frequently seen is that of dementia. Pinel [2] mentions a case of this kind, in which the insanity was cured by removal of the cancerous disease. Other nerve effects of cancer have also been noted, such as hyper-excitability of the muscles, increased reflexes, defective co-ordination, reaction of degeneration; with mild delirium, coma etc., in advanced cases. In connexion with symptoms of this kind, various minute lesions of the brain, spinal cord and meninges have been reported by Sänger,[3] Lubarsch,[4] Klippel,[5] and others, which have their counterparts in other severe anæmias.

A condition resembling diabetic coma—the *coma carcinomatosum*—is occasionally met with, of which Jaksch [6] has made a special study.

Alterations in the blood, that involve considerable reduction in its hæmoglobin, as in phthisis, anæmia etc., are usually associated—after a time—with widespread *fatty degeneration*, the result of impaired oxidation from diminished supply of oxygen. The cancerous cachexia is no exception to this rule. The parts most obviously thus affected, I have found to be, the liver, aortic arch, kidneys, large arteries, heart etc.; but microscopical examination shows that similar changes are almost universal. The anorexia and constipation so frequently met with, are largely due to changes of this kind, affecting the liver and the gastro-intestinal mucosa.[7] I have found that the liver is more frequently thus affected, in an extreme degree, than any other organ; it happened thus in 17 out of my 44 breast-cancer necropsies, and in 21 out of my 78 uterine-cancer necropsies.

From the general malnutrition consequent on the cancerous toxæmia, the *bones* suffer as well as the other structures. Great interest attaches to these little studied changes, which require to be carefully discriminated from the lesions produced by cancerous dissemination, with which most pathologists have confounded them. According to my experience, the

[1] *Bull. de la Soc. des Méd., etc., de Jassy*, 1894.
[2] *Traité de Path. Cérébrale*, p. 224.
[3] *Neurologische Centralblätter.* December 1, 1901.
[4] *Zeitschr. f. klin. Med.*, Bd. xxxi., S. 389. [5] *Arch. gén. de Méd.*, January, 1899.
[6] *Wien. med. Woch.*, 1883, Bd. xxxiii., S. 473 and 521.
[7] Fenwick, Medico-Chirurgical Transactions, London, vol. xlviii., p. 267.

bones most frequently thus affected in a marked degree are the ribs, sternum, femur, cranial bones, humerus, and vertebræ. These, when affected, still retain their normal size and shape; but they are lighter and more fragile than they should be, so that they are easily fractured. Campbell's [1] interesting experiments show, that their breaking strain is very low indeed—often even four times less than the normal. There is thinning of the cortex, with increased size of the medullary canal, the cancelli and Haversian canals being much enlarged and filled with diffluent medulla, hence the undue porosity. The ends of the long bones are specially apt to be affected in this way. Altogether the indications point to defective deposition of new bone to replace the loss by absorption, as the proximate cause of the condition.

Somewhat similar skeletal changes have been observed in many chronic wasting diseases, in the insane, in the aged, in pregnant women, in chronic phosphorus-poisoning etc.

Owing to this fragility of the bones, spontaneous fractures are easily determined—in the absence of any cancerous dissemination; of this I have met with several instances.[2]

It seems probable that the affection is in some way connected with alterations in the blood-forming properties of the red marrow; and it is a fact, that the bones most frequently thus affected are just those in which hæmatopoietic functions are normally most active. In this form of mollities, I have often noticed that the medulla has a gelatinous, diffluent aspect, very different from its normal appearance. According to Villy [3] and others, there is increase of the red marrow at first, with disappearance of the fat cells; and subsequently gelatinous degeneration supervenes. Somewhat similar changes have been produced experimentally in animals, by repeated bleedings; and in pernicious anæmia analogous conditions occur.

According to Rommelacre,[4] F. Müller [5] and others, the amount of urea in the urine of cancer patients, is decidedly below the normal, independently of alimentation, indicating lessened excretion of nitrogenous matter, owing to the great demands on the albuminous constituents of the body for the manufacture of new cells.

While the nitrogen distribution of normal urine comprised 96 per cent. urea, 1·8 per cent. uric acid, 1·2 per cent. $NH_3$, and 0·6 to 0·8 per cent. extractives, Töpfer found that the nitrogen of the urine of cancer patients comprised less than 80 per cent. urea, 1 to 5 per cent. uric acid, 0·2 to 13 per cent. $NH_3$, and 13 to 23 per cent. extractives.

The most constant of this group of changes seems to be the relative increase of the nitrogen of the extractives.

Most investigators report that the excretion of nitrogen in cancer patients is much in excess of the amount taken with the food; and the like is also alleged of the mineral salts.

[1] *British Medical Journal*, 1895, vol. ii., p. 776.
[2] For details and references to other cases of this kind, *vide* my book on "Diseases of the Breast," 1894, p. 215.
[3] *Journal of Pathology and Bacteriology*, January, 1898, p. 69; and May, p. 229.
[4] *J. de Méd. de Bruxelles*, 1883-1884.
[5] *Zeitschr. f. klin. Med.*, 1889, Bd. xvi., S. 496.

According to some authors there is relative increase of uric acid; but this is seldom a marked feature, and it is often wanting.

Another feature of the urine of the cancerous is its progressive demineralization, especially in respect to chlorides and phosphates. Noorden maintains that this diminution of chlorides is due to lessened intake of sodic chloride; and according to some authors the phosphates may be unaltered or even increased.

F. Müller reports having found slight degrees of albuminuria of common occurrence in the cancerous; and albumoses may also be met with.

An excess of acetone has been noticed by Argenson and others; while Lewin[1] has found its aromatic substances notably increased; and F. Müller an augmentation of the urobilin.

Gaudier and Hilt have lately shown, that the urine of the cancerous is more toxic than normal urine; and, in operated cases, they have found that this toxicity disappeared, after the removal of the local disease. Meyer[2] comes to the same conclusion; and finds also that the splenic substance is highly toxic; while Griffiths[3] claims to have isolated from the urine of cancerous patients a highly poisonous ptomaine, not present in normal urine.

A remarkable fact that may be mentioned here, is the rarity with which *amyloid degeneration* is associated with cancer; among my 44 breast-cancer necropsies there was not a single instance of it, and it was met with only in 4 cases, out of my 78 uterine-cancer necropsies. In each of these instances, the spleen was involved, and in 2 the liver as well.

It is now generally recognized, that suppuration and ulceration are not essential precursors of amylosis, which may ensue from a variety of morbid conditions that seriously interfere with nutrition—*e.g.*, chronic intermittent fevers, malarial cachexia, large uterine and ovarian tumours, rachitis, gout etc.

In this connexion, great interest attaches to Krawkow's experiments, on the artificial production of amylosis, by the injection of cultures of *Staphylococcus pyogenes aureus;* whence the author concludes, that the amyloid material is a result of the constant poisoning and lowering of the organism by microbic products.

The comparative rarity and the slight intensity of the febrile complications of cancer, is a noteworthy feature of the disease; but, occasionally fever is found, independently of ulceration or of any inflammatory process, just as sometimes happens after simple fracture of a long bone. In such cases, it may be ascribed to some deleterious substance entering the circulation—in the one case from the tumour, in the other from the damaged tissues—and subsequently affecting the heat centre, so as to cause fever.

Fever is specially apt to be met with in cancer cases, complicated by intra-osseous metastases.

[1] *Deutsche med. Woch.*, 1905, Bd. xxxi., S. 218.
[2] *Zeitschr. f. klin. Med.*, Bd. xxxiii., S. 663.
[3] *C. R. de l'Acad. des Sci.*, Paris, t. cxviii., p. 1350.

When cancerous growths ulcerate and the wounds are invaded by microbes, the ordinary symptoms of septic infection are added to those of the cancerous cachexia. Considering the putridity that characterizes these ulcerating cancers, especially when the uterus is the part affected, septic complications are remarkably rare; but, no doubt, in certain cases, they contribute their quota to the ensemble of symptoms.

Hæmorrhages and suppurations further impoverish the blood, and weaken the patient.

At length, if not cut off by some inter-current complication, death results from *asthenia:* it was thus that 64 of 90 uterine-cancer cases, that ran their natural course under my observation, terminated; and, in 24 of 40 fatal cases of breast cancer, the end was similarly determined.

It will be gathered from the foregoing review, that no indications of a specific cancer toxin are forthcoming: altered conditions of the blood, secondary diseases of the organs which play an important part in metabolism, diminished intake of food, superadded microbic infections etc., suffice to account for all such changes as have hitherto been discriminated.

## CHAPTER XXII

## QUASI-MALIGNANT PSEUDO-PLASMS

THE enterprise of modern surgery, with its frequent exploratory operations from which no part of the body is exempt; the greater frequency and thoroughness of modern post-mortem examinations; the increasing accuracy of death certification, with corresponding improvement in the national mortality statistics; and finally, the wonder caused by the immense number of reputed "cures," of all kinds, for cancer—duly attested by skilled practitioners and specialists, with histological verification etc., etc. —although those best capable of judging doubt if a single case of cancer has ever been really cured: all these concomitant events have at length revealed to practitioners the truth, long known to those who have specially studied the disease, that the differential diagnosis of cancer is a difficult matter, in which mistakes are of frequent occurrence.

Having arrived at this conclusion, the question naturally arises as to the chief causes of these diagnostic fallacies. In a general way, they may no doubt be ascribed to the fact, that there is no pathognomonic sign of cancer; nor does the disease produce any specific symptoms, indicative of its presence. Hence, every case has to be judged, by carefully weighing the ensemble of the indications available for diagnostic purposes. To do this effectually, a much more intimate acquaintance with the pathology and life-history of cancer is required, than is at present possessed by practitioners—whether holding hospital appointments or not; and, it is equally important, to be keenly alive to the many morbid conditions which simulate cancer, as to which practitioners have also almost everything to learn.

The sources of these diagnostic fallacies may be divided roughly into two classes:—(1) those very numerous cases in which cancer is simulated by some non-malignant morbid condition; and (2) a smaller class of cases, in which—owing to the latency or misleading nature of the symptoms—the presence of the malady is overlooked.

It is with the former group of cases, that we are here chiefly concerned. Owing to the immense extent of the subject, it will be impossible in the brief space available, to do more than direct attention to this order of fallacies, by some general observations relating thereto, coupled with reference to a few typical illustrative instances.

As a rule, the chief non-malignant morbid conditions likely to simulate cancer, may be grouped as follows:—(1) many "chronic inflammatory" affections; (2) various syphilitic lesions; (3) a very large number of tuberculous manifestations; (4) many mycotic affections; (5) various parasitic and microbic lesions; and (6) a large class of pseudo-parasitic maladies, of which the causative agent is unknown or only dimly apprehended.

The professional mind is so obsessed with the erroneous idea that any tumour, not obviously inflammatory, appearing in persons over forty, is almost invariably malignant; that further exploration of its nature is seldom seriously undertaken. This is specially noticeable, in the case of tumours of the female breast; indeed, a prominent cancer surgeon lately stated his belief, that every tumour of the breast in women over forty, "whether cyst, fibroma or what not," sooner or later underwent "malignant degeneration," and so required extirpation forthwith. As I have previously adduced evidence to show, such a belief has no scientific validity, although it may be very convenient for surgeons. The truth is, that of 100 women seeking surgical advice, on account of tumour-like swellings of the breast believed to be malignant, it will be found that less than half of the total are really of this nature.

Of the pseudo-cancerous lesions, the largest proportion will undoubtedly prove to be "chronic inflammatory" indurations. By far the commonest manifestation of this kind likely to be mistaken for cancer, is the chronic circumscribed mastitis—the *induratio benigna* of the old authors. I have seen several instances in which this condition has been mistaken for cancer, and the breast amputated; and illustrative specimens of this kind may be found in most pathological museums.

In a case under my own observation, the patient was a large, obese woman, aged fifty-seven, the mother of two children, with a lump in her left breast of seven years' duration. The breasts were voluminous. Near the periphery of the axillary segment of the affected part, was a very hard, nodulated mass, the size of a tangerine orange, covered by a thick layer of fat. The overlying skin was adherent and dimpled; but the tumour was movable over the subjacent parts, and the nipple was normal. There was no pain or tenderness. Several axillary glands were enlarged. An exploratory incision into the tumour, revealed a dense, whitish fibroid aspect, just like that of ordinary scirrhous cancer. Even after its complete removal, the aspect of the divided tumour was very cancer-like; but the section did not "cup," and it was juiceless. Histological examination showed dense fibrous tissue, containing numerous nuclei, in which a few acinous and tubular mammary glandular structures were embedded: but there were no signs of cancer. The enlarged axillary glands were also free from cancer. When last seen, three years after the operation, this patient was in excellent health, and free from any return of the disease.

Here the unusual absence of pain and tenderness, together with the presence of dimpling of the skin, and all the usual signs of cancer except retraction of the nipple, prevented the recognition of the real nature of the disease, although the chronicity of the lesion excited doubt as to its cancerous nature.

Even various inert foreign bodies, embedded in the breast, such as needles, pins, bits of glass, small sequestra from the subjacent ribs, which have separated by quiet necrosis etc., may give rise to chronic indurations, simulating cancer. There is a specimen of this kind in the Hunterian Museum, presented by Astley Cooper (No. 67 of the Pathological Series), which is thus described : " Part of a woman's breast removed on account of what was supposed to be a chronic tumour. A needle 2 inches long is embedded in the mammary gland, the surrounding substance of which is indurated : the needle is covered with rust, but is in other respects perfect."

Another form of chronic mastitis, likely to be mistaken for cancer, is the diffuse, cirrhosing variety, which produces retraction of the nipple and overlying skin, with wasting and deformity of the part, similar to that characteristic of atrophic scirrhus.

Periductal mastitis, the *maladie noueuse* of French authors, the *plexiform fibroma* of the Germans, and the "lobular hypertrophy" of English writers, which is generally attended with sclerosing fibrosis, often simulates cancer, although less frequently than the foregoing types.

It is a common mistake of clinicians to suppose, that tuberculous lesions of the female breast are of exceptional rarity ; they are really of commoner occurrence than is generally believed ; and, when in the form of chronic indurations, and as cold abscesses, they are often mistaken for cancer.

By way of illustration, the two following remarkable cases are of exceptional interest :—

1. I was requested by a medical friend to see an unmarried lady, aged forty, with a swelling in her breast of some months' duration, which she attributed to an accidental blow from a child's elbow. On examination, I found near the periphery of the axillary part of her left breast, a nodular lump, the size of a marble, surrounded by irregular, ill-defined thickening and induration. Although the lump was hard, yet the degree of induration seemed to me to fall short of that usually associated with scirrhous cancer. The tumour was painful, and on manipulation decidedly tender. The nipple was stunted and transversely grooved ; but, both were alike in these respects, and neither was retracted. The skin over the tumour was decidedly drawn upon, so that when a cutaneous fold was pinched up it dimpled ; but the tumour was movable on the subjacent parts. The adjacent axillary glands were enlarged. I also detected slight lobular thickening in the opposite breast. The patient had chronic cough, with a small amount of muco-purulent expectoration, and moist râles could be heard over the upper lobe of her left lung. In early adult life, she had hæmoptysis ; and subsequently, for many years, active phthisical disease. Some years ago, however, this became quiescent ; and her general health subsequently greatly improved. Three of her sisters had died of phthisis. Under these circumstances—relying mainly on the pain and tenderness of the swelling, the comparative rapidity of its formation, its ill-defined margins and moderate hardness, as well as on the slight lesions in the opposite breast—I was able to assure the patient that the tumour was almost certainly not cancerous. Moreover, relying on the presence of tuberculous disease in the lungs, and the history of it in her family, I expressed the opinion that in all

probability the mammary lesion was also of tuberculous origin; and recommended local and general anti-tuberculous treatment.

I was then for the first time informed, that the lady had previously consulted a medical man elsewhere, who had pronounced her disease to be cancerous; and had made every arrangement for amputating the breast the following week. I consequently sent this gentleman a polite note, stating the circumstances, and what I had recommended. He wrote a huffy letter to the patient's friends, making light of my diagnosis and suggestions for treatment, recommending that the operation should nevertheless be proceeded with as arranged, and deprecating the painful predicament in which the patient was placed. Fortunately, this advice was *not* followed; and, after a few months' treatment, the disease entirely disappeared.

2. At the Pitié Hospital in Paris, I witnessed the following instructive case, in which a tuberculous abscess was mistaken for cancer of the breast:—

A healthy-looking multipara, aged thirty, applied to Verneuil on account of a mammary tumour of six months' duration, which she first noticed about a month after her last confinement. On examination, there was found, deeply seated in her left breast, an exceedingly hard, irregularly shaped mass, about the size of an orange. At one spot the tumour was softer than elsewhere, and gave indications of indistinct fluctuation. The adjacent axillary glands were enlarged. The nipple was not retracted, nor was the overlying skin dimpled; and there was only slight pain and tenderness. Basing his remarks on this case, the learned professor gave to the assembled class an eloquent address, on the differential diagnosis of mammary cancer, with special reference to its discrimination from cold abscess. He concluded, from the extreme hardness of the tumour, and the enlargement of the axillary glands, that the case before them was an undoubted example of scirrhus, although some of the usual clinical features were wanting. In accordance with this view, he proceeded, before the whole class, to amputate the breast with the thermo-cautery knife. In the middle of the operation, a large abscess cavity was opened, out of which gushed a considerable quantity of thick yellow pus. The eloquent professor looked grave and puzzled. He proceeded with his operation, however, including removal of the axillary glands. The patient made a complete and rapid recovery. Subsequent histological examination of the parts removed, showed no signs of cancer; but all the indications of a cold, tuberculous abscess.

It would be easy to multiply such cases as the foregoing; and cancer-like lesions, due to pseudo-tuberculosis of this part, have often been reported.

I have not the slightest doubt, that a certain proportion of these quasi-malignant indurations of the female breast, are of syphilitic origin; I have seen cases of this kind, in which the affection took the form of gummatous tumour, and others in which it was of a more or less infiltrating nature.

In making the diagnosis of the various non-malignant, tumour-like lesions, likely to be mistaken for cancer, some surgeons, and notably

Bryant,[1] attach great importance to cysts. According to my investigations, cysts rarely originate in the breast, independently of neoplasia; that is to say, cysts of sufficient size to require notice, in respect to the question of the differential diagnosis of cancer. An analysis I have made of 2,397 mammary tumours, consecutively under treatment at four large metropolitan hospitals, shows that only 63 were cysts, or 2·6 per cent.

Certain cysts, especially when tense and deeply seated—like cold abscesses—occasionally acquire stony hardness, and otherwise simulate cancer; but, such cases are far from common. For one such cyst resembling cancer, at least a dozen tumour-like swellings of inflammatory origin (chronic mastitis, tubercle, syphilis, cold abscess etc.), easily mistakable for cancer, will be met with.

With regard to the discrimination from malignant disease of fibro-adenoma, villous papilloma, the effects of trauma—including foreign bodies embedded in the part, galactocele, and slight glandular thickenings associated with neuralgia etc.—nothing further than the mere mention of such contingencies is here necessary.

The numerous cases of actinomycosis in human beings, reported during the last quarter of a century, show that this disease is by no means rare in mankind; and, almost every part of the body, has been found affected. Over a score of cases of this kind have already been reported in the breast, in some of which the symptoms of malignant disease were closely simulated; so that, in making the diagnosis of quasi-malignant tumours, this malady has also to be borne in mind.

A few cases of mammary mycosis fungoides, having much resemblance to sarcoma, have also been reported (Lancéreaux, Leslie Roberts etc.).

Even small, tense, hydatid cysts, which are decidedly rare in the breast, have been mistaken for cancer.

Under a variety of curious names of their own special invention, which serve as a cloak for their lack of understanding of the pathology of the maladies, dermatologists have brought together a chaotic medley of quasi-malignant cutaneous pseudo-plasms, which are constantly mistaken for true malignant tumours.

A large number of these seem to be the outcome of tuberculous disease, in some of its protean forms, most of them belonging to the lupus family, with its many aberrant variations.

The "epithelioma-like" histological appearances of sections of lupus-ulcers, was long ago demonstrated by Lang, Busch and others; but, these histological findings, do not justify the diagnosis of "cancer."

When, however, the lupus-malady departs from its ordinary course, producing chronic carneous excrescences; then, such histological findings, are thought to justify the diagnosis of "lupus-cancer," as in cases reported by Bayha and others. From such an interpretation I entirely dissent; and, in the absence of clinical signs of malignancy, I believe that such lesions would be more correctly described as *lupus hypertrophicus*. Certainly, they have no real similitude with any form of epithelioma or sarcoma.

[1] *Lancet*, 1900, vol. i., p. 1201.

Another malady belonging to a kindred category, is the *sarcoma melanodes cutis* (Kaposi's disease), in which multiple "sarco-carcinomatous" nodes form on the face or other exposed parts of the body, often in quite young children, more than one member of a family often being affected.

It seems to me an abuse of terms to describe such a malady as sarcoma, on account of certain histological appearances of sections of the tumour; when the *ensemble* of the indications available for diagnostic purposes point in quite another direction.

A good many cases of multiple, quasi-malignant pseudo-plasms of the skin, have also been described as "sarcoma," because round, spindle, or myeloid cells have predominated in their structure: this type of disease fairly often undergoes more or less complete resolution—either spontaneously, or as the result of various remedial agencies—and is otherwise about as unlike any form of real sarcoma, as any malady could possibly be. Most of such tumours are probably of tuberculous, or mycotic origin.

As examples of this morbid condition reference may be made to a case described by S. Mackenzie,[1] in which a man aged fifty-four, was subject to livid nodular growths on the hands and feet, which on histological examination presented a sarcoma-like appearance—"multiple pigmented sarcoma." Four years after amputation of the right leg for this malady, the remaining lesions spontaneously retrogressed and disappeared.

In R. Crocker's case,[2] a man aged thirty-seven who had suffered for some time from arthritic troubles, developed a number of small crimson tumours on the hands, head, back and other parts, which rapidly increased in size. Nearly a year later, when the patient was taking salicylate of soda for the arthritic condition, these tumours began to dwindle, and finally most of them disappeared. The histological appearances of sections of the tumours, resembled myeloid sarcoma.

Other cases of this kind have been described by Köbner,[3] Kaposi etc., as examples of cutaneous sarcomatosis; by Shattock and Ballance [4] as "withering sarcoma"; by Cotterill and Welsh [5] as "syphiloma"; by Bristowe [6] as "tubercle"; and by many authors as "granuloma fungoides," "lymphadénie cutanée" etc.

"Duhring's neoplasm," in which fungating growths like tomatoes form in the skin, some of which shrivel and disappear from time to time, while new ones arise, should probably be classed in the same category; for, the *ensemble* of the malady is entirely different from true sarcoma, with which it has hitherto been confounded. As Duhring [7] himself says: "Better let it be named and unclassified, than be placed and become fixed wrongly."

Somewhat similar fungating tumours, some of which undergo spontaneous resolution, also occur in that interesting malady *mycosis fun-*

[1] *Lancet,* 1896, vol. ii., p. 470. [2] *Ibid.*
[3] *Berlin. klin. Woch.*, 1883, No. 2.
[4] Allbutt's "System of Medicine," 1896, vol. i., p. 215.
[5] *British Medical Journal,* 1900, vol. ii., p. 1444.
[6] *Ibid.*, 1892, vol. ii., p. 996. [7] *Archives of Dermatology,* January, 1880.

*goides*, which is so often confused with sarcoma. These growths are almost certainly of microbic origin, although no specific organism has yet been detected.

This is the class to which the so-called "withering sarcomata" belong; which are so often cited, as evidence of the curability of sarcoma.

Quite lately the important discovery has been made, that certain blastomycetes, oidia etc., are capable of causing quasi-sarcomatous lesions of this kind, as well as chronic cutaneous ulcers, like epithelioma. We owe this discovery chiefly to the experiments of Sanfelice and his followers, although Busse and Curtis had previously reported remarkable instances of the kind in human beings, as mentioned in a previous chapter,[1] and I particularly recommend that these cases should be carefully studied in the present connexion; for, in all probability, many of these quasi-malignant, cutaneous pseudo-plasms are thus caused.

Granulomatous, cutaneous pseudo-plasms, simulating malignancy, due to mould fungi aspergillosis, coccidiosis, botryomycosis etc., have also been reported.

Actinomycotic, quasi-malignant, tumour-like lesions of the skin, have also been demonstrated in many cases.

Quasi-epitheliomatous ulcers of the skin, often resembling rodent ulcer, due to tubercle, syphilis, chronic seborrhœa, and mycotic lesions, are no great rarities; and these are the cases that the X rays cure.

Moreover, there can be no doubt that quasi-cancerous lesions of the skin, are often caused by atypical syphilitic manifestations. Esmarch[2] has specially shown us the great frequency of lesions of this type: thus, he has had, in his own practice, more than forty patients sent to him for operation with supposed malignant growths, which subsequently underwent complete resolution, under antisyphilitic treatment. The special and general medical publications teem with illustrative cases of this kind.

Even ordinary chronic inflammatory cutaneous lesions, such as "chronic seborrhœa," may originate quasi-malignant, tumour-like swellings; and it is probable that the whole keloid group is due to causes of this kind.

Moreover, it is alleged that certain drugs, such as arsenic and iodide of potassium—when unduly pushed or in cases of idiosyncrasy—may cause quasi-malignant, tumour-like lesions.

If then, in parts of the body so easily accessible to physical examination as the female breast and the skin, we nevertheless encounter these numerous sources of fallacy, in making the diagnosis of malignant disease, it may readily be imagined, how much these difficulties are enhanced in parts less favourably situated for thorough exploration, but nevertheless equally liable to these quasi-malignant lesions.

Some remarkable examples of quasi-malignant, disappearing tumours, in connexion with the stomach, have been reported.

In Jessett's[3] case, a large tumour of this kind connected with the pylorus, completely disappeared after gastro-enterostomy; although,

[1] Chapter X. [2] *Verhandl. d. deutsche Gesellsch. f. Chir.*, Kongress, 1895, Bd. xxiv.
[3] *Lancet*, 1901, vol. i., p. 1005.

when microscopically and macroscopically examined, it presented the appearance of hard cancer. Similar instances have been met with by Warthin and Spitzley,[1] Hasse [2] and Bennett.[3]

Examples of quasi-malignant intestinal lesions due to tubercle, have been described by Bezançon and Lapointe,[4] Moynihan [5] etc.; and, to actinomycosis, by Borelius [6] etc.

Some time ago G. Smith [7] specially called attention to certain solid, quasi-malignant, intra-abdominal tumours, which subsequently underwent complete resolution; and these he showed were due to chronic inflammatory lesions. Many similar instances have since been investigated, with the like result, although in some there has been a diagnosis of sarcoma or carcinoma, based on histological findings: R. Johnson,[8] H. Snow,[9] Warthin and Spitzley,[10] M. Robson,[11] Janeway [12] and others, have reported examples of this kind.

Some striking cases of these disappearing, quasi-malignant tumours in the orbit, have been met with by S. Snell,[13] Panas and others.

These few typical examples suffice to show the necessity, for giving more attention to the differential diagnosis of malignant disease in the clinics, than has hitherto been customary; and, no harm would be done, if it were generally admitted, that we are still far from knowing all that is to be known about cancer, even in its clinical aspect.

As I have previously mentioned, pseudo-plasms of the kind here under consideration, are of even more frequent occurrence in animals, than in humanity; and they seem to attain their maximum of frequency in fishes. In the vegetable world, they are also of great frequency, especially in the form of galls.

[1] *New York Medical News*, 1901, vol. lxxix., p. 443.
[2] *Arch. f. path. Anat.*, 1897, Bd. cxlix., S. 236; also *ibid.*, 1896, Bd. cxlvi., S. 209.
[3] "Cancerous and Canceroid Growths," 1849, pp. 39 and 212.
[4] *La Presse Méd.*, May 18, 1898.
[5] Transactions of the Clinical Society of London, 1907, vol. xl., p. 31.
[6] *Nord. Med. Arkiv.*, 1903, No. 6.
[7] Transactions of the Medico-Chirurgical Society, London, 1894, vol. lxxvii., p. 139.
[8] *British Medical Journal*, 1903, vol. i., p. 915.
[9] *Ibid.*, 1897, vol. i., p. 1414.
[10] *New York Medical News*, 1901, vol. lxxix., p. 443.
[11] *British Medical Journal*, 1908, vol. i., p. 425.
[12] Trans. of the Association of American Physicians, 1907, vol. xxii., p. 170.
[13] *Lancet*, 1897, vol. i., p. 238.

## CHAPTER XXIII

## INFLAMMATION, ULCERATION, RETROGRESSION, AND SPONTANEOUS CURE

Cancerous tumours, once formed, live and are nourished like normal parts of the body; yet they, in return for the nutriment thus supplied, contribute nothing serviceable—functionless and redundant, their relationship to the rest of the organism, differs but little from that of parasitism.

The biology of cancers, like that of normal parts, is conditioned mainly by the inherent properties of their constituent cells; and, in a less degree, by their blood-supply. Hence, the same elementary pathological disturbances may be witnessed in them, as in the normal parts—*e.g.*, congestion, inflammation, suppuration, gangrene, necrobiosis, ulceration, and the degenerative metamorphoses. That long-continued augmentation of the blood-supply, may accelerate the growth of cancers; and diminished blood-supply retard it, is I think indisputable. The marked exacerbation of mammary cancers, consequent on pregnancy, traumata, and various irritants, are examples of the former effect; while many very chronic forms of the disease, are probably largely dependent upon the latter. I am, however, far from believing that most of the striking irregularities in the rate of growth of cancers, can be accounted for by circulatory disturbances. The inherent properties of the neoplastic cells themselves, here play the leading part.

The most frequent anatomical cause of *congestion* and *inflammation* of cancers, is obstruction of their venous circulation, which, as I have previously mentioned, so often happens during the progress of their growth; and, the defective formation of their bloodvessels, no doubt favours these conditions.

Cancers are, however, less frequently subject to acute inflammation, than might *a priori* be expected. When this does occur, not only the neoplasm itself, but also its immediate surroundings may be affected. Such attacks, which are mostly of septic origin, often greatly accelerate the progress of the disease. Subacute inflammations, are commoner than the acute ones. Cohnheim believes that inflammatory conditions of the surrounding tissues weaken their capacity for resistance, and so favour the spread of the disease. Inflammation of cancer may terminate in resolution, suppuration, or gangrene.

*Suppuration* is rare, but it undoubtedly does occur.

Habermaas [1] has related a curious case, in which the breast was ampu-

[1] *Beitr. z. klin. Chir.*, 1886, Bd. ii., S. 44.

tated for a tumour—accompanied by enlarged axillary glands—which was believed to be tuberculous. On examination of the part, after removal, this diagnosis appeared to be correct, for there was revealed a pus-containing cavity, surrounded by caseous-looking masses. Histologically examined, however, these proved to be, not tuberculous, but cancerous.

Gross [1] mentions the case of a woman, whose breast he had amputated for a cancerous tumour, the size of a hen's egg. On section of the growth after removal, he found in it an abscess full of greenish pus. H. Marsh [2] and Shield [3] have described several cases of suppurating malignant tumours. However, the suppuration of primary malignant tumours is so exceptional, that when this condition is met with in a quasi-malignant new formation, it raises the presumption of mycotic infection, tubercle or syphilis, rather than of cancer.

Instances of the association of mammary cancer with suppurating galactocele, with tubercle, and with pseudo-tubercle, have also been reported.

A more frequent ending than suppuration, is *gangrene* and sloughing. This is generally only partial, but exceptionally the whole tumour may fall into a state of slough.

Ulcerated cancers are more prone to gangrene than others. Sometimes the sphacelus is determined by injury, or by septic infection such as erysipelas ; but usually there is no obvious cause.

Obliteration of the veins is its chief determining factor ; hence, it is generally of the moist kind, but the dry form is not unknown. Gangrene is always a harmful complication ; severe local inflammation and pain attend it, together with profuse, fœtid discharge, pyrexia and much constitutional disturbance ; and the danger from sepsis is very great. Gangrene may be followed by almost complete cicatrization ; but, as the disease is never entirely destroyed, recurrence is inevitable—at any rate, I cannot cite a single instance of cure by gangrene.

For the following account of a case, in which a cancerous breast separated by sloughing, consequent on erysipelas, I am indebted to Dr. Richmond of Warrington.

A single woman, aged forty-five, had scirrhous cancer of the left breast, and cancerous glands in the axilla. While waiting for extirpation, a sharp attack of erysipelas supervened, involving the diseased mamma etc. In consequence of this, the diseased breast sloughed clean away, leaving a healthy granulating surface, which rapidly cicatrized. There was no return of the disease in this locality ; but, the undestroyed part in the axilla spread rapidly, and the patient died soon afterwards, with symptoms of internal dissemination.

Billroth has reported an instance in which a mammary cancer of seven years' duration, and the size of an apple, exfoliated spontaneously by dry gangrene, the wound cicatrizing rapidly. When shown at the Berlin Medical Society (1893) shortly afterwards, the cicatrix was quite sound, but its edges were raised and hard.

1 "American System of Gynæcology," vol. ii.
2 St. Bartholomew's Hospital Reports, 1887, vol. xxiii., p. 147.
3 *British Medical Journal*, 1900, vol. ii., p. 1259.

Like their physiological prototypes of the mamma, sebaceous glands and epidermis, the cells of breast cancers are short-lived. Hardly ever can one examine a cancerous tumour without discovering some of its cells in *fatty degeneration*, and this eventually ends in their complete disintegration. Such conditions have little or nothing to do with circulatory disturbances ; they occur as regular stages in the evolution of the disease, owing to molecular changes inherent to the cells themselves. To this cause we must attribute the tendency of cancers to spontaneous *ulceration*, at a certain stage of their development ; which may begin, as Hunter pointed out, either superficially or deeply. In the former circumstance, the growing tumour becomes adherent to the overlying skin, which gets thinned and excoriated, and eventually yields, leaving the surface of the neoplasm exposed, and this consequently ulcerates ; in the latter, the changes leading to ulceration begin in the substance of the neoplasm, and open outwards. Ulceration once started, usually tends to spread indefinitely ; yet a cancerous neoplasm is never completely destroyed in this way, for the disease progresses faster than the ulcerative process. Many cancers never ulcerate ; this was the case in twelve of the forty-three fatal mammary cases under my observation : ulceration rarely supervenes in this form of the disease, until the malady is fairly advanced.

The *typical ulcer* of cancer presents as an irregularly rounded, excavated, crater-like cavity, with hard, raised, swollen, craggy edges, which are usually everted ; and to these edges the surrounding skin is always adherent. It appears as if scooped out of the subjacent cancerous growth, hence its hardness ; hence also its extensive union with adjacent structures.

Cancerous ulcers of long standing, often present quite a different aspect to the foregoing : they are shallow, with slightly raised and sinuous edges, the base comparatively smooth, and covered with small granulations, which in places have a florid and almost healthy appearance. A thin parchment-like layer of indurated cancerous tissue underlies the whole affected area, and binds it to the subjacent structures. Such ulcers not infrequently cicatrize more or less extensively ; they may even be covered over by scar tissue, and remain for considerable periods in a non-progressive, quiescent state. These favourable changes are closely allied to those which determine the atrophic form of the disease ; but I cannot cite a single case of definitive cure by ulceration, although hundreds of alleged " cures " of this kind of lesion have been reported.

Epithelioma of the lower lip, has a special proclivity to heal over in this manner, the primary disease shrinking in size so as to be hardly noticeable ; and yet, after a time, secondary growths appear in the adjacent lymph-glands. Interesting examples of this have been reported by Merkens,[1] Hendry,[2] Freeman and others.

Similar conditions are also met in connexion with cutaneous cancers, especially in connexion with the penis, scrotum, vulva etc.[3]

Moreover, it must be borne in mind, that in all these localities quasi

[1] *Deutsche Zeitschr. f. Chir.*, November, 1902.
[2] *New Zealand Medical Journal*, March 31, 1903.
[3] For further reference to cases of this kind, *vide* Chapter XIX., p. 426.

malignant chronic ulcerative lesions, with a healing tendency, are often met with of tuberculous, syphilitic, or other non-malignant causation.

Some interesting examples of this kind, affecting the tip of the nose, have lately been described by Du Castel [1] and Crouch.[2]

Various forms of abnormal *fat formation* in malignant tumours, arise in connexion with circulatory disturbances, influencing the metabolism of their cells. Thus, parts where growth is exceedingly active, sometimes exhibit a kind of local *embonpoint*; that is to say, fat globules are separated and deposited in them, which would have been oxidized and removed, but for the local supply of nutritive materials being in excess of metabolism.

Here mention may be made of the fact that an organ containing a cancerous tumour, such as the breast, sometimes gets surrounded by abnormal fatty growth, owing to circulatory disturbances of this kind (capsular lipomatosis).

Localized fatty degenerations, due to deficient blood-supply through venous congestion, inflammation, thrombosis, arteritis etc., are of frequent occurrence. When the arteries are seriously interfered with, considerable areas of the neoplasm may thus be rendered necrobiotic. In such cases, not only the cells, but the stroma also may degenerate—as in the so-called *lipomatous cancers*.

In like manner arise the areas of caseous softening, sometimes seen irregularly scattered throughout cancerous tumours, as in the so-called *caseating cancers*. The ultimate fate of such lesions is chiefly dependent upon the subsequent cellular changes; if these go on to complete disintegration, the resulting products may be absorbed and completely disappear, or they may liquefy and form cysts, or caseate and eventually even cretify.

A healthy-looking, childless, married woman, aged thirty-three, under Bryant's [3] care, had an ulcerated cancerous tumour of the right breast, of stony hardness, and firmly fixed to the pectoral muscle. The tumour was of six years' duration, and it had been ulcerated for four years. The ulcer was the size of the palm of the hand—its edges being nodular and crumbly. The axillary glands were enlarged and hard. Operative interference was declined. Fifteen months later, the tumour was obviously smaller and harder; and several pieces—the size of nuts—had shed from its edge. Six months later it had still further diminished, and much of the original tumour had crumbled away. Some discrete cancerous tubercles now appeared, in the adjacent skin over the sternum. In the course of the next year, the tumour continued to contract and to throw off pieces. The cutaneous tubercles notably diminished, and the axillary glands got smaller and harder. Two years later, the ulcer had almost completely cicatrized—a puckered linear scar was all that remained, in which were a few small, hard nodules. The tubercles in the adjacent skin had completely disappeared. A year later, all that re-

[1] *Medical Press and Circular*, 1901, vol. ii., p. 623.
[2] *Bristol Medico-Chirurgical Journal*, September, 1903, p. 23.
[3] "Diseases of the Breast," 1887, p. 142; for other cases of this kind *vide* St. Bartholomew's Hospital Reports, 1891, vol. xxvii. (Masterman).

mained of the original disease was a single nodule, the size of a hazel-nut, in the scar. The axillary glands were hardly perceptible. The patient's general health was unimpaired. One and a half years later, she again came under observation ; during this interval several fresh tubercles had appeared in the skin, near the cicatrix, and had subsequently disappeared, so that only two small ones now remained. The patient considered herself quite well. She died five and a half years later, of some pulmonary complication, without any obvious increase of the local disease having taken place. Altogether the disease had lasted for nearly nineteen years.

There is in the Hunterian Museum,[1] a remarkable specimen of atrophic epidermoidal cancer of the base of the tongue, in which nearly the whole organ disappeared during the course of the disease, the disappearance being unaccompanied by ulceration.

Unfortunately, even with these retrogressing forms of cancer, the malady continues to spread at the growing edge.

The so-called "calcifying epitheliomata" of the skin etc., which may exfoliate, and are sometimes cited as examples of cancer cured by calcification, are essentially non-malignant formations of adenomatous nature.

The changes produced in cancerous tumours by colloid, myxomatous, and atrophic metamorphoses, constitute special well-recognized varieties of the disease, which need not be further particularized here.

I have before mentioned, that the characteristic feature of cancer is its tendency to persist indefinitely, and to increase continuously. Yet indications are not wanting of occasional spontaneous *retardation* and *arrest* of the disease, and even of its *retrogression ;* but I cannot cite a single instance of its complete spontaneous cure. Nevertheless, in face of the following facts, I think it would be rash altogether to deny the possibility of such a fortunate occurrence.

The extreme chronicity of certain cases of cancer shows, that the increase of the disease may sometimes be so exceedingly slow, as hardly to be appreciable. Instances of this kind are of more frequent occurrence in the breast than is generally believed ; and, what is still less appreciated is, that the great majority of such cases are morphologically indistinguishable from ordinary acinous cancer (scirrhus), being neither of the atrophic nor of the colloid variety, although both atrophic and colloid cancers exhibit, in a high degree, the tendency to chronicity and retardation.

Instances of this kind may be met with in the malignant tumours of all parts of the body.

The following are some of the best examples of these retrogressing cancers known to me :—

A young woman consulted Osler,[2] for a lump in her breast of more than four years' duration. The part was removed shortly afterwards, together with the tumour, which was "undoubtedly cancerous in nature." Two years later she was seen, with symptoms of choroidal metastasis ; and, some months later, recurrent nodules appeared in the other

[1] No. 2,273, Pathological Series. [2] *Canadian Practitioner*, 1901.

breast, with loss of power of the legs, and indications of dissemination in the liver. Morphine was prescribed, but nothing else was done. Some time later, when Osler saw her again, he was surprised to find that the secondary nodules in the breast had disappeared, she had regained the power of walking, and the vision of the affected eye had much improved.

In another case by the same doctor, after the removal of a cancerous tumour from the breast, the patient developed "girdle pains" and pain in the legs, with paraplegia. Great weakness supervened, and she appeared to be moribund. Then gradual improvement set in spontaneously; many of the recurrent nodules disappeared; as also did the pains and paraplegia. She was able to get up and walk about, although she still had "a stiff back."

It would be interesting to know the final results in these cases.

In a case lately described by MacKay,[1] the patient was a spinster, aged thirty-seven, with cancer of the breast, which retrogressed in the penultimate stage; when the patient was in a hopeless, collapsed, and "half-starving condition," with double hydrothorax etc.

Gould [2] has reported two somewhat similar instances.

In the first of these, the patient, aged forty-one, had her left breast removed, together with the axillary glands, for cancer of over a year's duration. Five months later, symptoms of double pyosalpinx having appeared, both ovaries and tubes were removed by laparotomy. Two and a half years later she was seen again, when there were recurrent nodules in the mammary region and axilla, as well as in the supraclavicular region. The liver was large and nodular, and there was hydroperitoneum, as well as a discharging sinus in the laparotomy scar. She was in a very feeble and emaciated condition. No further operative or other special treatment was adopted. In the course of the next few years, the recurrent nodules of the chest-wall disappeared, except a single small one near the scar; the enlarged axillary and supraclavicular glands also dispersed; the liver became much smaller and the hydroperitoneum diminished. Meanwhile her general health so much improved, that she got up and left the hospital.

In another case, the patient was a single woman, aged forty-seven, whose left breast had been amputated nine years before, for a tumour of two years' duration, which on microscopical examination after removal, was found to be "typical scirrhous cancer." Two years after this operation, there was recurrence in the left axilla, which was removed. Two years later there was recurrence in the left chest, and above the right mamma. About this time the menopause supervened. The recurrent disease was now again extirpated; but, soon afterwards, fresh recurrent nodules formed in both mammary regions, in the axillæ, and in the lower part of the neck on each side. She suffered from shortness of breath, orthopnœa and symptoms of invasion in the right lung and pleura. About this time a lump appeared at the upper part of the right

[1] *British Medical Journal*, 1907, vol. ii., p. 138.
[2] Clinical Society's Transactions, London, 1897, vol. xxx., p. 205; also *Clinical Journal*, 1902, vol. xx., pp. 96 and 120.

femur, which underwent spontaneous fracture. Her general condition was now such, that she was considered to be *in articulo mortis.* No special treatment of any kind was adopted. Strange to relate, in the course of a few months, her condition greatly improved; she lost the orthopnœa, and most of the recurrent nodules disappeared. The femoral tumour vanished, and the fractured bone consolidated. In this improved condition, she has remained for several years.

In a case by J. Hutchinson,[1] the whole of the right mammary region was occupied by a thin, smooth, parchment-like, glossy scar, which extended backwards beyond the mid-axillary line; its edge being slightly elevated, hard and sinuous, like that of rodent ulcer. Near this large, scar-like area, were several small, isolated patches of similar appearance. The left mammary region was affected in the same way. Near the anterior border of the left axilla was a subcutaneous nodule, the size of a hazel-nut. This was the only situation in which the growth had any thickness. Nowhere was there even a trace of ulceration. There were a few hard glands in each axilla, none of them larger than horse-beans.

The disease began as a hard tumour in the right breast, thirteen years previously, and it only subsequently invaded the left breast. Never at any stage had it ulcerated. The patient consulted Hutchinson on account of pulmonary complication of recent development, which was thought to be due to fluid in the right pleura. After the chest had been tapped several times, without any fluid being discovered, it became evident that the dulness was due to intra-thoracic solid growth. The patient died about two months later from this cause; but there was no necropsy.

The two following cases, by Broca,[2] are also of much interest:

1. A woman, aged sixty-nine, who died in hospital with secondary cancer of the liver. She was admitted with extensive chronic ulceration of the mammary region, which had supervened on hard cancer of the breast of many years' duration. The ulcer was shallow; its edges but slightly raised; and it had commenced to cicatrize in several places. On microscopical examination of the part after death, it was found that the whole of the cancerous growth had been destroyed by ulceration, except a single nodule—the size of a hazel-nut—near the centre of the ulcer.

2. A lady, who when first seen had an irregular scar in the mammary region, in connexion with which there was a small, hard, cancerous nodule of some months' growth. She said that, fifteen years previously, she first noticed a tumour in her breast, which subsequently ulcerated; and, after a time, healed up without any operation ever having been done. Some time afterwards, however, a fresh growth appeared in the cicatrix, which later on ulcerated; but, again the ulcer healed spontaneously, after which the present recurrence set in. She refused operative treatment. The disease subsequently progressed so rapidly, that she died of it a few months later.

Some instances of retrogression, as in the two following cases by

[1] *Archives of Surgery*, April, 1891, vol. ii., No. 8, p. 354.
[2] "Traité des Tumeurs," 1866, t. i., p. 240.

Billroth [1] and Walshe,[2] coincide with its outbreak in remote parts of the body. These seem greatly to have impressed the old surgeons, who erroneously regarded them as true metastases, which term they henceforth applied to all systemic disseminations.

1. A woman, aged forty, with an infiltrating cancerous tumour of the left breast, the size of an apple, who refused operation. One year later, she again came under treatment with paraplegia, due to dissemination of the disease in the vertebræ. The former tumour, with its surrounding infiltration, had completely disappeared ; in its place nothing remained but a flat, indurated, superficial scar, which was slightly excoriated.

2. A very cachectic woman, with non-ulcerated, hard cancer of the breast, of two years' duration, was seized with violent cephalalagia, followed by apoplectic symptoms with hemiplegia. At about the time of this attack, the mammary tumour notably diminished ; and, when she died, ten weeks later, it had almost completely disappeared. The *necropsy* revealed a cancerous tumour, the size of a nut, in the brain.

In the next case, by Paget,[3] subsidence of the cancerous disease, coincided with the active progress of pulmonary tubercle.

The patient was only twenty-five years old, yet she had a large, hard, cancerous tumour of the breast. The disease had progressed very rapidly, its total duration being only three months. The overlying skin and nipple were invaded. The axillary glands were enlarged and hard. The breast was amputated ; after which the swelling of the axillary glands subsided. Six months later, there was recurrence in the mammary region and in the axilla. In the former situation, the disease made rapid progress ; numerous tubercles formed in its vicinity, which coalesced, and eventually ulcerated. Thus it progressed for a year, when the ulcer began to cicatrize ; and, in the course of six months, it had almost completely healed. The axillary disease also subsided, one hard lump alone remaining of what had been a large cluster of hard glands. Meanwhile, however, the patient had emaciated and lost strength ; and she died, about two years after the operation, and six months after the cancer had so nearly healed, of tuberculosis of both lungs. On careful examination of the mammary region after death, a thin, flattened, nodular *plaque* of extremely hard and dense cancer, was found beneath the old scar, binding it to the pectoral muscle. In the axilla was a single hard cancerous gland ; and the liver contained several equally hard growths.

Sigg [4] and others have met with similar cases.

Perrion [5] has seen mammary cancer subside, after an operation for goitre followed by much suppuration ; and Jahr [6] has reported the retrogression of mammary sarcoma, after artificially induced delivery.

Several instances of these "retrogressing cancers" have been met with in connexion with the uterus, among others by Sänger, Rokitansky, Klob and Scanzoni ; but, no well-substantiated example of spontaneous

[1] *Deutsche Chir.*, 1880, Lief. xli., S. 106.
[2] "Nature and Treatment of Cancer," 1846, p. 110.
[3] "Lectures on Surgical Pathology," 1853, vol. ii., p. 337.
[4] *Corresp.-blatt. f. schweizer Aerzte,* April 15, 1891.
[5] *Rev. Méd. de la Suisse Romande,* t. xi., p. 195.
[6] *Berlin. klin. Woch.*, July 30, 1894, S. 726.

cure is known to me, although in some cases of "corroding ulcer" (*epithelioma uteri superficiale*) the anatomical evidence of the disease was very slight, as in the following case under my observation :

A single woman, aged sixty-one, who had never been pregnant, having suffered for nearly four years from symptoms of uterine cancer, died of asthenia, no operation having been done. At the necropsy, the body was found to be extremely emaciated. The whole of the uterus had disappeared, with the exception of its thickened peritoneal covering, which circumscribed a pouch, the size of a small orange, into which the vagina led directly. The interior of this cavity and the upper part of the vagina, presented a softish, granular, yellowish-green, smooth discharging surface, in connexion with which no induration or infiltration was apparent. The adjacent parts seemed equally free from cancerous disease. Into the front of this cavity the bladder opened, and into its back the rectum, each by a rounded opening, the size of a florin. The atrophied ovaries were adherent to the outside of the peritoneal pouch representing the uterus. This pouch was further strengthened by the matting together of the adjacent pelvic structures, so that no perforation into the peritoneal sac had occurred. There was slight double hydronephrosis. No infiltrated glands could be discovered, nor were there any secondary cancerous deposits elsewhere. The other organs were normal. Microscopical examination of the wall of the eroded cavity, revealed scanty fibrillar tissue, densely infiltrated with small round cells (lymphocytes). Embedded here and there in this structure, were lobular epithelial masses, consisting of solid aggregations of small, irregularly shaped, epithelial cells, presenting no signs of epidermic evolution, and no "nests." Many of the cells were in advanced stages of granular degeneration. These structures did not penetrate deeply. Beneath them was a thin layer of the fibro-myomatous tissue of the uterine wall, infiltrated with small round cells.

Rokitansky's case [1] of alleged cure by sloughing and ulceration, with the subsequent formation of a funnel-shaped scar, is by no means convincing.

Téallier [2] has witnessed marked retardation of uterine cancer during lactation ; while, by Blanchard [3] and Fleury,[4] remarkable examples of the arrest and retardation of the disease have been reported, in patients reduced to the last extremity of debility by the malady.

In cases of intra-abdominal malignant disease, Bidwell,[5] B. Clarke,[6] H. Snow [7] and others, have observed marked amelioration, after simple exploratory laparotomy. Beatson's cases of regression of mammary cancer after oöphorectomy, probably belong to this category. Malignant tumours have also been known to retrogress after partial removal, as in cases reported by Richardson,[8] Munro Smith [9] and others. Similar

[1] "Pathological Anatomy" (English translation), 3rd edit., vol. iii., p. 495.
[2] "Du Cancer de la Matrice," Paris, 1836, p. 227.
[3] *Marseille Méd.*, 1869, t. vi., S. 997.
[4] *Arch. Méd. Belges*, Bruxelles, 1863, t. xxxii., p. 98.
[5] *Lancet*, 1897, vol. ii., p. 1346. [6] *Clinical Journal*, February 6, 1907, p. 264.
[7] *British Medical Journal*, 1897, vol. i., p. 1414.
[8] *Annals of Surgery*, December, 1898, p. 741.
[9] *Bristol Medico-Chirurgical Journal*, March, 1900.

results have ensued after thyroid medication, tuberculin injections, injections with the toxins of erysipelas, and in the various phases of serum-therapy.

Many interesting particulars relating to cases of this kind, will be found in the publications of H. Mohr [1] and Lomer.[2]

Reviewing these various typical examples of arrest and retardation of the disease, it appears that they may be grouped under the following headings :

1. In the penultimate stage of the cancerous cachexia, and in most illnesses causing great wasting and exhaustion (*e.g.*, phthisis), cancerous growths may become stationary and retrogressive.

2. Acute infective diseases may exert a similar retarding influence on the growth of malignant tumours, as is especially noticeable with erysipelas. Such remission of the disease as is noticeable after injections of the toxins of erysipelas, and Coley's fluid, may also be cited, in this connexion.

3. In another class of cases, similar results have followed various operative procedures, such as laparotomy, partial removal of the malignant tumour etc. To this category, Beatson's cases of retrogression of mammary cancer after oöphorectomy, probably belong ; and also the X-ray treatment, which seems to be effective as well through the local inflammatory action excited, as through concomitant changes in the blood, and the system in general, especially the sexual system. In this connexion it may be remembered, that it was formerly the custom to prevent wounds made for the removal of cancer, healing by first intention, under the impression that recurrence was thereby retarded.

4. Retrogression of the local disease, may coincide with the outbreak of fresh foci in remote parts of the body, as if there had been real metastasis.

5. In a considerable number of instances the growth of malignant tumours is arrested, without there being any obvious concomitant to account for it, other than extreme general debility.

It is quite evident, when we bear in mind the many various conditions with which the retrogression of malignant tumours is associated, that there can be nothing specific about it. Indeed, the only feature common to all such cases, is the extremely debilitated condition to which the patients are reduced ; and, I think there can be no doubt, that enfeebled vitality is the chief cause of such improvement as is noticeable. As Luschi and others have shown, in conditions of this kind, the glycogen and carbohydrates of the body are used up and attenuated, to such an extent, as to render active cell proliferation almost impossible. Such patients are, in fact, reduced to a state similar to that brought about by the starvation-treatment of cancer, as formerly practised with some success by Hufeland and others.

[1] *Therapeutische Monatschr.*, 1903, Heft 11 and 12.
[2] *Zeitschr. f. Geb. u. Gyn.*, Bd. l., Heft 2.

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